EUROGIN 2019 ABSTRACTS

FREE COMMUNICATION SESSIONS

FC 01 - HPV testing and genotyping (I)

#0360

8 - HPV testing

QUALITY ASSURANCE FOR HPV TESTING IN AUSTRALIA - THE FIRST TWO YEARS

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Background/Objectives: December 2017 marked a significant National Cervical Screening Program (NCSP) change, resulting in human papillomavirus (HPV) nucleic acid testing (NAT) replacing cytology as the primary cervical cancer screening method. HPV NAT was intended to identify the risk of developing cervical cancer, with limited HPV typing used to stratify risk. Subsequently, programs used to monitor quality assurance of tests necessitated modification as per testing guidelines. NRL introduced an external quality assessment scheme (EQAS) and quality control (QC) material in early 2017 to prepare for these changes. A review of the first year showed evidence of an expected adjustment to the new testing paradigm, and review of performance since then was carried out to assess whether the switch has now settled to routine quality assurance performance.

Methods: EQAS: NRL provided 8 EQAS distributions (5 since the HPV NAT transition). The samples were manufactured using digital droplet PCR (ddPCR), ensuring that samples with the same characteristics (concentration and genotype) could be compared between multiple distributions over a number of years. Participating laboratories were grouped for analysis based on the assay used (known as a "peer group"). The reported assay interpretations, reproducibility of detection and identification of different genotypes presented (16 and 18) were assessed. While the assays are qualitative, most report a cycle threshold (Ct) value, which was used to compare samples of the same concentration. QC: laboratories participating in NRL's Quality Control Program submit their results into EDCNet (developed by NRL). EDCNet also uses peer group analysis, providing individual laboratory performance against their peers. In addition, EDCNet collate and compares data on variation in assay reagent lots, instruments and operators, all known to impact on patient care.

Results: EQAS: Use of ddPCR (and therefore quantified material) allowed for scientific rigour in data analysis across multiple events provided since 2017. Participants submitted results from 12 different assays. They demonstrated accurate detection of materials provided at 10-fold dilutions and excellent repeatability based on the analysis of submitted Ct values. Challenging educational samples were also included, providing insight for manufacturers and participants on assay performance in different laboratory environments. QC: Over 15,000 QC results were reported since the transition for three different NRL QConnect HPV NAT QCs. QC differs from EQAS as it provides daily monitoring information. Variation in reagent lots, instruments and operators were all evident. Importantly, EDCNet data identified when the observed variation was of concern, considering that NAT on this scale was a new endeavour for NCSP laboratories.

Conclusions: The importance of meaningful quality assurance programs cannot be understated, especially when changing from a reactive to risk-based testing strategy as occurred with the Australian NCSP. Providing materials similar to clinical samples showed that sample preparation (and therefore operators) had a major impact on result variation. Assay reagent lots were also a common source of variation due to the complexity of chemistries in NAT assays. Improved knowledge of QC and EQAS data would aid laboratory staff and managers reinforce the importance of operating procedures and how consistent QC and EQAS performance translates to reliable patient results.

#0535

8 - HPV testing

HPV ONCOPREDICT: DEVELOPMENT OF A NOVEL DIAGNOSTIC TOOL ALLOWING ACCURATE DETERMINATION OF SAMPLE CELLULARITY AND NORMALIZED GENOTYPE-SPECIFIC VIRAL LOAD

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Background/Objectives: Cervical cancer (CC) kills 330,000 people annually and requires persistent infection with high-risk Human Papillomavirus (hrHPV) for its development. European guidelines advocate the use of hrHPV DNA tests for CC prevention in women over the age of 30 years. Moreover HPV testing on self-collected vaginal and urine samples has been proposed in order to increase women's participation to screening programs. Most presently available hrHPV tests however do not provide quantitative sample cellularity assessment as a measure of sample adequacy, or hrHPV viral load. HPV OncoPredict is a new in-vitro diagnostic tool allowing accurate sample adequacy assessment and hrHPV Genotype-Specific Viral Load (E6/E7 DNA) determination developed as part of a Horizon 2020 SME Instrument Project (SME Instrument Grant GA 806551). The aim of this pilot study is to evaluate the performance of HPV OncoPredict prototype on cervical as well as on self-collected vaginal and urine samples.

Methods: Clinician-collected cervical (CCC), Self-Vaginal (SV) and First-Void Urine (FVU) samples were collected from 100 women undergoing colposcopy at San Gerardo Hospital, Monza, Italy. Colli-Pee (Novosanis), L-Shaped and Vaginal FLOQSwabs (Copan) were used respectively for FVU, CCC and SV collection. CCC and SV were resuspended in 20 mL and 5 mL (SV5) of ThinPrep (Hologic) respectively; an additional SV aliquot is tested following a further dilution 1:4 (SV20). Nucleic acid extraction from 1 mL of each sample type was performed using NucliSENS easyMAG (bioMérieux); CCC and SV extracts were then eluted in 100 ul and FVU in 40 ul of buffer. HPV OncoPredict prototype was then used to assess samples' cellularity and normalized hrHPV genotype-specific viral load.

Results: Preliminary data using HPV OncoPredict prototype indicate an adequate cellularity for all sample types (mean human cellularity values of 1.01E+05, 3.62E+05, 1.85E+05, 4.87E+05 cells/mL for CCC, SV5, SV20 and FVU respectively). Mean normalized viral loads overall ranged from 2.43E+00 to 2.04E+04 GU/10E+04 human cells, with differences in viral loads being observed among different hrHPV genotypes as well as sample types.

Conclusions: HPV OncoPredict prototype preliminary evaluation has shown promising results for the accurate determination of both sample cellularity and hrHPV viral loads in both cervical and self-collected samples. Differences in the normalized viral loads observed between hrHPV and sample types however suggest that further clinical studies are required to determine genotype-specific viral load clinical cut-off values, also based on the sample type.

References: This project is conducted in collaboration with Genefirst as part of the EU funded programme (Project no 806551).

#0580

11 - Genotyping

SYSTEMATIC LITERATURE REVIEW ON THE UTILITY OF EXTENDED GENOTYPE DETECTION FOR HPV TYPE 31: PREVALENCE AND RISK FOR CIN3 DISEASE

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Background/Objectives: Advances in the screening and detection of cervical disease have been greatly aided by the inclusion of HPV testing along with cytology to identify patients at risk for CIN2+ disease. The role of extended HPV genotyping to further define risk for CIN2+ in the screening population was evaluated in this literature review.

Methods: We undertook a systematic review of literature to compare relative contribution of HPV genotype 31 toward the development of cervical cancer. The analysis included searching PubMed, PubMed Central, Database for Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and the IARC HPV Information Centre from 2000 through 2019 for relevant cross sectional analyses, controlled clinical trials and observational studies. In addition, a supplemental review was conducted by searching retrieved article references. Metrics of clinical utility for the discrete detection of HPV type 31 included the following: prevalence rates in cervical disease (cervical squamous cell carcinoma; endocervical adenocarcinoma; ASC-US+ cytology); enrichment in CIN3+ cases; progression rates; odds ratio for detection of incident CIN3+; and 3-5 year risk for CIN3+ detection associated with HPV type 31.

Results: 2830 articles were initially identified by the various search strategies. Over 200 articles were screened for inclusion/exclusion criteria and 70 articles were retrieved for data review and comparison. Finally, 40 articles were selected for data analysis. Within this analysis, HPV type 16 was consistently identified as the most oncogenic HPV virus in terms of prevalence in cervical carcinoma; enrichment in CIN3; and 3 year risk for developing CIN3. Likewise, HPV type 18 was also associated with a significant risk for CIN3. The extracted data indicated that HPV type 31 had a similar risk profile to that of HPV type 18 with respect to odds ratios; progression rates; and 3-5 year risk for development of CIN3. In contrast to squamous lesions, the prevalence and oncogenic potential of HPV 31 in cervical adenocarcinoma appeared lower than that of HPV 18.

Conclusions: In high-risk HPV positive patients, across NILM, ASC-US and LSIL cytology cases, the 3-year risk for CIN3+ development associated with HPV type 31 was comparable to the risk contributed by HPV type 18. Given the importance of HPV 18 detection in cervical cancer screening paradigms, a comparable risk between HPV 31 and HPV 18 merits further analysis. Additional clinical studies appear warranted to evaluate the role and utility of HPV type 31 identification within cervical cancer screening paradigms.

#0202

11 - Genotyping

HIGH RISK HPV INFECTION AMONG WOMEN OLDER THAN 25 YEARS IN A NORTH-EAST REGION OF MEXICO BY PCR DNA TEST

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Background/Objectives: Cervical cancer in Latin America and México persists as an important cause of death among young women despite the efforts in screening strategies, continuing to be one of the most common cancer in the women population; In Mexico, although it´s incidence has declined is estimated at 20 cases per 100,000 women. the cervical cancer remains the second cause of death among malignant neoplasms in young women. There is a close association between the high-risk HPV persistent infection and the development of cervical cancer, therefore it is important to establish the prevalence of this infection among each population. The aim of this study was to stablish the prevalence of the high-risk HPV infection among women older than 25 years in a north-east region of Mexico by a PCR DNA test.

Methods: This was a cross-sectional descriptive study conducted from June 2011 to July 2014 at a specific north-east area of Mexico, including 9 states of the country. A chain polymerase reaction DNA test for genotyping of high-risk HPV was performed with the Roche® COBAS 4800® in women of 25 to 64 years old in a screening scenario. The test detected individually the 16 and 18 subtypes and a pool of the other 12 HR HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 y 68).

Results: A total of 55,382 women were included, with a prevalence of all HR HPV types of 10.1% (n=5,594) of which the most common result was the other 12 HR HPV pool with a 7.65% (n= 4237) prevalence, in contrast with a lower prevalence of the HPV 16 and 18 subtypes: 1.19% (n=659) and 0.40% (n=221) respectively, and a 0.86% prevalence (n=476) of coinfection of more than one subtype of the HR HPV. Only a 0.43% of the tests were invalid.

Conclusions: The 10.1% of prevalence on HR HPV in this population it´s similar to other reported studies. This was one of the studies that included more women in Latin America and the results can be generalize to the Mexico´s women population above 25 years old (CI 95% 10.09-10.11). We found a higher prevalence of non 16 and 18 HPV subtypes; however, this test was not able to identify which of the other 12 HR HPV were more prevalent. The low rate of invalid tests demonstrates the efficiency of the technique and equipment used. The HPV DNA test is a reliable and effective tool to identify women with the high-risk HPV infection among Mexican women.

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#0297

20 - New technologies

HPV genomics and cancers

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Background/Objectives: To comprehensively characterized the human papilloma virus DNA associated with any carcinomas, we developed a Capture-NGS method to identify at once the HPV genotype, the HPV status (absence, episomal, integrated), the viral load, the viral-host chromosomal DNA junctions, as well as the associated genome rearrangements at the insertion locus (deletion or amplification). This technology and the initial analysis of 72 cervical carcinomas (frozen biopsies and circulating DNA) was reported by Holmes et al., Npj Genomic Medicine (2016) 1, 16004; doi:10.1038.

Methods: Biopsies Next Generation Sequencing: illumina Capture HPV ; PacBio Capture HPV; Whole Genome Sequencing

Results: Our powerful Capt-HPV NGS genomic approach has been successfully transferred to ther NGS platforms and medical centers. Today, at the Institut Curie, 2x150bp paired-end Illumina Capt-HPV has been applied to large cohort of cervical, anal and, head and neck tumors, comprising a total of >700 tumors. The comparison of the above HPV genomic parameters will be presented, specially emphasising highly significant differences observed among tumor localizations.Furthermore, following our Capt-HPV observation of the multiplicity of HPV-chromosomal junctions in certain tumor samples (>2 chromosomally clustered or scattered hybrid junctions), we pursued their characterization by developing a Capture HPV PacBio method and in parallel performed Whole Genome Sequencing (WGS). It allows to analyse long chromosomal fragments (>10 Kb) and resolve the structural complexity of the insertion events in cervical tumor samples. Pairing of tumor and constitutive WGS samples also allowed to search for other somatic gene mutations and the genome rearrangements.

Conclusions: We performed multiple NGS approaches to characterize the genome of Cervical, anal and head&neck tumors demonstrating various HPV status differences. Our development of HPV genomics technologies, adaptable to other virus-associated diseases, will be presented, while reporting their use in the molecular comparison of various HPV associated tumors. Perspective of application in diagnosis and follow-up of patient treatment in clinical is an additional topic to be discussed.

References: Holmes et al., Npj Genomic Medicine (2016) 1, 16004; doi:10.1038.

FC 02 - HPV prophylactic vaccines (I)

#0432

5 - HPV prophylactic vaccines

CONTINUING EVOLUTION OF GENDER-NEUTRAL HPV VACCINATION: AN UPDATE ON NATIONAL IMMUNIZATION PROGRAMS AND EVIDENCE GAPS ASSOCIATED WITH GNV POLICY DEVELOPMENT AND PROGRAM IMPLEMENTATION

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Background/Objectives: Background: Growing recognition of Human Papillomavirus (HPV)-related disease burden is driving the expansion of HPV vaccination programs from female-only to gender-neutral (GNV) in countries around the world. This study aimed to provide an update on evolution and status of GNV programs globally, as well as current understandings of the economic, political, social, and epidemiological drivers of policies for GNV programs.1

Methods: Methods: We updated a review from Shrestha et al., 2018 using official government websites, PubMed, Google Scholar, and Cochrane Reviews, to identify publications of interest from 2010 to 2019. Eligible literature included peer-reviewed research studies, commentaries, systematic reviews, grey literature, and media reports.

Results: Results: Forty-one countries and territories were identified with established GNV programs: 16 in North/South America, 17 in Europe and 8 in the Middle East-Africa/Asia-Pacific. The updated review identified 97 additional publications, of which we extracted data from 78. Among the countries with established GNV programs, several have published evidence documenting their decision to implement GNV programs (e.g., Croatia, Germany, and the United Kingdom). The key factors considered during policy decision-making included the health and financial impacts of HPV-related disease burden, low female vaccination rates, and cost-effectiveness data. The primary reason for establishing GNV programs included an increasing recognition of HPV as a gender-neutral public health problem, supported by the data emerging from early adopters (e.g., Australia, Austria, Canada, and USA). Limited literature exists surrounding specific barriers to establishing a GNV program.

Conclusions: Conclusion: Over the years, there has been a steady increase in the number of countries expanding HPV vaccination programs to include males in order to improve population-level HPV infection control. However, additional information on key drivers influencing policy development and program implementation is needed to help overcome potential barriers inhibiting expansion decisions globally. Future studies evaluating these factors would be valuable to countries that have not yet sought to include males in their national HPV vaccination programs.

References: [1Shrestha, A. et al. Identifying Evidence Gaps in Understanding Facilitators and Barriers associated with Expanding HPV Vaccination Programs to Males. Poster presented at: International Papillomavirus Conference, 2018 Oct 2-6; Sydney, Australia]

#0191

5 - HPV prophylactic vaccines

GENDER-NEUTRAL HPV VACCINATION IN NATIONAL IMMUNIZATION PROGRAMS OF LATIN AMERICA AND THE CARIBBEAN, 2011-2019

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Background/Objectives: Background: Countries are increasingly expanding HPV vaccination programs to include boys to confer direct protection, to improve population-level HPV infection/disease protection, and to strengthen vaccination program resilience. Objectives: The objective of this analysis is to describe the evolution and main characteristics of HPV Gender-Neutral Vaccination (HPV-GNV) National Immunization Programs (NIPs) in Latin America and Caribbean (LAC).

Methods: A targeted literature review was conducted in PubMed, SciELO and LILACS databases, including articles written in English, Spanish and Portuguese between January 2006 and May 2019. Grey literature was searched, including websites of relevant government and non-government organizations and conference proceedings in May 2019. The main parameters analyzed were year of HPV vaccine introduction (female/male), target age, vaccine schedule, delivery strategy, estimated eligible population size of 10-14-year-old males with vaccine access in LAC (calculated using Population Prospects of United Nations), and vaccine coverage rate (VCR).

Results: As of May 2019, 40 of 51 LAC countries/territories have HPV vaccine in their NIPs (78.4%), with HPV-GNV programs adopted by 15 (29.4%). Ten of them have adopted multi-age cohort vaccination introduction. The expansion to an HPV-GNV program occurred, on average, 3.3 years after the introduction of female vaccination. The main primary target population is 9-14-year-old girls/boys using two-dose schedule (0-6 months), except for Chile (0-12 months), via school-based or community health-centers programs. 38.2%(10.7 million) of 10-14-year-old boys that live in LAC countries have access to HPV vaccination. Some countries have implemented HPV-GNV strategy for special populations from 9 to 26 years old: individuals living with HIV (men who have sex with men up to 40 years old), transplant recipients, oncology patients, and sexually assaulted individuals. The HPV VCR data varied widely across LAC regarding methodology and 2 dose-series completion in males and females (20.1-58.2% and 49.9%-78.8%).

Conclusions: The number of countries extending HPV vaccination to boys in LAC has increased quickly since 2016, doubling from 7 to 15. Most have adopted multi-age cohort vaccination, targeting 10-14-year-old males. Although the methodology to calculate VCR are heterogeneous, they indicate that VCR in males is lower than in females. The use of a standard methodology to calculate HPV VCR in LAC would provide more accurate data to implement regional goals and achieve desired outcomes.

References:

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#0294

5 - HPV prophylactic vaccines

IMMUNOGENICITY OF AN ESCHERICHIA COLI-PRODUCED HPV BIVALENT VACCINE IN FEMALES AGED 9-45 YEARS

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Background/Objectives: Human papillomavirus (HPV) types 16 and 18 cause 70% of cervical cancer cases globally. A new HPV-16/18 bivalent vaccine expressed by Escherichia coli has been proven to be safe and highly efficacious against high-grade precancer lesions related to HPV-16 and HPV-18 in adult women1 and non-inferior in girls aged 9-17 years as compared to 18-26 women2. Antibody level is an important index to evaluate the effect of vaccination. Here, we combinedly analyzed the antibody levels induced by HPV-16/18 bivalent vaccine in healthy females aged 9-45 years enrolled in the above two trials.

Methods: A multicenter, randomized, double-blind, phase III trial and an immunobridging trial of the new HPV-16/18 bivalent vaccine were conducted in China. In the phase III trial, women aged 18-45 years were age-stratified and randomly assigned to receiving 3 doses of the test vaccine (n=3689) or control (hepatitis E) vaccine (n=3683) at months 0, 1 and 6. In the immunobridging trial, girls aged 9-14 years were randomized to receive 2 doses at months 0 and 6 (n=301) or 3 doses at months 0, 1 and 6 (n=304). Females aged 15-26 years received 3 doses at months 0, 1 and 6 (n=374). Serum samples were collected at month 0 and month 7 to assess IgG antibody responses against HPV-16 and HPV-18 by enzyme-linked immunosorbent assay (ELISA). Analyses for immunogenicity were performed in PPS cohorts, which included all participants who received all the scheduled vaccine doses according to the protocol, were negative for IgG antibody against the relevant types of HPV at entry, and an additional criteria was requested for the PPS cohort of the phase III trial, being negative for the relevant types of HPV DNA from day 0 through month 7.

Results: Combined the data from PPS cohorts of the phase III and immunobridging trial, seroconversion rates of HPV-16 and HPV-18 were 100% (3100/3100) and 99.9% (3641/3644) at month 7. The geometric mean concentrations (GMCs) of IgG antibodies to HPV-16 and HPV-18 induced by 3 doses HPV vaccination decreased with age (Figure 1). In the age group of women with the lowest GMC, the GMC for HPV-16 and HPV-18 were 566.8 IU/mL and 202.0 IU/mL, which were 80 times and 43 times higher than the mean antibody level acquired from natural infection (7.1 IU/mL and 4.7 IU/mL). In those receiving 2 doses, antibody response seemed to be almost the lowest in 9 years and then increased to the peak level in 10 years, although the data was limited, it implies immunization program starting from girls older than 10 years.

Conclusions: The E coli-produced bivalent HPV-16/18 vaccine induced robust type-specific antibody responses in females aged 9-45 years, the antibody levels were inversely associated with age.

References: 1. Qiao YL, Wu T, Li RC, et al. Efficacy, safety, and immunogenicity of an Escherichia coli-produced bivalent human papillomavirus vaccine: An interim analysis of a randomized clinical trial. Journal of the National Cancer Institute 2019, Epub ahead of print. 2. Hu Y, Guo M, Li C, et al. Immunogenicity noninferiority study of 2 doses and 3 doses of an Escherichia coli-produced HPV bivalent vaccine in girls vs. 3 doses in young women. Science China Life sciences 2019, Epub ahead of print.

Figure 1. Vaccine-induced type-specific IgG antibodies in females aged 9-45 years

#0274

5 - HPV prophylactic vaccines

REAL-WORLD EVIDENCE CONFIRMS AS04-HPV-16/18 VACCINE SUSTAINED CROSS-PROTECTION AND OVERALL PROTECTION REGARDLESS OF TYPE

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Background/Objectives: Is the overall protection induced by the AS04-adjuvanted HPV-16/18 vaccine (AS04-HPV-16/18v; Cervarix) regardless of HPV oncogenic type and the cross-protection confirmed in real-world settings and sustained over time?

Methods: Evidence review of HPV vaccination programs with AS04-HPV-16/18v.

Results: The pivotal vaccine efficacy (VE) trial for AS04-HPV-16/18v (PATRICIA; NCT00122681) demonstrated 93.2% (95% confidence interval [CI]: 78.9; 98.7) overall efficacy regardless of HPV oncogenic type against cervical intraepithelial neoplasia grade 3 or greater (CIN3+) 4 years after vaccination.[1] Significant VE against CIN2+ lesions associated with the non-vaccine types HPV-31 (89.4%, 95% CI: 65.5; 97.9), HPV-33 (82.3%, 95% CI: 53.4; 94.7) and HPV-45 (100%, 95% CI: 41.7; 100) was also confirmed.[2] Ten years post vaccination, passive follow-up of the Finnish cohort in PATRICIA trial showed continued VE of AS04-HPV-16/18v against CIN3+ irrespective of HPV type.[3] At the 11-year follow-up of the VE trial in Costa Rica (NCT00128661), significant cross-protection was observed against prevalent infections with combined HPV-31/33/45 (VE: 60.5%, 95% CI: 45; 72) which was similar to the VE observed at year 4 and 7.[4] In Scotland, 7 years after the initiation of the vaccination program, vaccine effectiveness against prevalent infection with vaccine types HPV-16/18 was 89.1% (95% CI: 85.1; 92.3) and with non-vaccine types HPV-31/33/45 was 85.1% (95% CI: 77.3; 90.9) in women vaccinated at age 12-13 years.[5] This was further translated into protection against high-grade lesions and an 89% reduction of CIN3+, irrespective of HPV type in the lesions, in the same birth cohort.[6] Significant decreases in infections with some non-vaccine types (HPV-31, -33, -45, -52 and -58 alone or combined) have been reported up to 8 years post vaccination across countries using AS04-HPV-16/18v in their national program.[7-13]

Conclusions: Available real-world evidence strongly suggests that cross-protection of AS04-HPV-16/18v against some non-vaccine types is sustained over time. Ongoing long-term surveillance programs are confirming the high overall protection against cervical disease regardless of type with AS04-HPV-16/18v.[6,13] Funding: GlaxoSmithKline Biologicals SA.

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#0436

5 - HPV prophylactic vaccines

IMMUNOGENICITY AND SAFETY OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS (QHPV) VACCINE IN CHINESE GIRLS (AGED 9-19 YEARS) AND YOUNG WOMEN (AGED 20-26 YEARS): AN OPEN-LABEL, PHASE 3, IMMUNOBRIDGING STUDY

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Background/Objectives: The recombinant qHPV vaccine protects against HPV6/11/16/18-related infection and disease, and was approved for use in women (aged 20-45 years) in China in 2017. To support licensure in girls, the Chinese regulatory authority mandated a local, post-marketing study comparing immunogenicity in Chinese girls (aged 9-19 years) with young women (aged 20-26 years). The study consists of a Base (Day 1-Month 7) and Extension stage (Month 7-Month 60); we report immunobridging and safety data from the Base stage.

Methods: In this open-label, Phase 3 study (NCT03493542), Chinese girls and young women received 3 doses of qHPV vaccine (Day 1, Month 2, Month 6). Antibody responses were assessed in serum samples collected at Day 1 and Month 7 by competitive Luminex immunoassay. The primary and key secondary objectives were to demonstrate non-inferiority of anti-HPV geometric mean titers (GMTs) and seroconversion at Month 7, respectively, in girls compared with young women. The non-inferiority criterion with respect to GMT required the lower bound of the two-sided 95% confidence interval (CI) of GMT ratio (girls vs. young women) to be >0.67 for each HPV type, and the criterion with respect to seroconversion required the lower bound of the two-sided 95% CI in differences (girls minus young women) to be >-5% for each HPV type. Immunogenicity analyses were based on the per-protocol population. Safety (injection-site and systemic adverse events [AEs] and serious AEs [SAEs]) was evaluated as a secondary objective.

Results: Of 766 Chinese girls and young women enrolled, most (97.9%) received all 3 vaccine doses (girls, 98.2%; young women, 97.7%). At Month 7, robust anti-HPV GMT responses were observed, and 100% of participants seroconverted to each vaccine HPV type. Prespecified statistical criteria with respect to GMTs and seroconversion rates were met for all vaccine HPV types, demonstrating that antibody responses at 1 month post-Dose 3 in girls were non-inferior to those in young women (all P values <0.0001). Girls and young women had similar safety profiles. Injection-site AEs and systemic AEs (Days 1-31 post-vaccination) were reported by 36.6% and 49.3% of girls and 40.7% and 54.8% of young women, respectively. SAEs were reported by 6 (1.6%) girls and 10 (2.6%) young women; none were considered vaccine-related. No deaths were reported and no participants discontinued vaccination due to AEs.

Conclusions: Anti-HPV immune responses induced by a 3-dose regimen of the qHPV vaccine in Chinese girls (aged 9-19 years) were non-inferior to those observed in young women (aged 20-26 years). The qHPV vaccine was generally well tolerated in these populations.

#0455

5 - HPV prophylactic vaccines

IMMUNOGENICITY AND SAFETY OF A NINE-VALENT HUMAN PAPILLOMAVIRUS VACCINE IN WOMEN 27-45 YEARS OF AGE COMPARED WITH YOUNG WOMEN 16-26 YEARS OF AGE: AN OPEN-LABEL PHASE 3 TRIAL

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Background/Objectives: Clinical studies have demonstrated the efficacy of the nine-valent human papillomavirus (9vHPV; HPV 6/11/16/18/31/33/45/52/58) vaccine against infection and disease in women 16-26 years of age. We conducted a study comparing 9vHPV vaccine immunogenicity and safety in women 27-45 years of age vs. women 16-26 years of age.

Methods: Participants received 9vHPV vaccine on Day 1, Month 2 and Month 6. Blood was collected for immunogenicity testing by competitive Luminex immunoassay on Day 1 and Month 7. A distinct per-protocol immunogenicity population was assessed for each of the 9 HPV types. Geometric mean titers (GMTs) and seropositivity rates at Month 7 for anti-HPV 6/11/16/18/31/33/45/52/58 were summarized. The primary objective of the study was to demonstrate non-inferiority of anti-HPV 16/18/31/33/45/52/58 GMTs in women 27-45 years of age vs. women 16-26 years of age. A >2-fold decrease in immunogenicity had to be ruled out to demonstrate non-inferiority in women 27-45 years of age compared with women 16-26 years of age. The safety evaluation included injection-site and systemic adverse events (AEs) for 15 days after any vaccination and serious AEs during the entire study.

Results: 1212 participants were enrolled (570 women 16-26 years of age; 642 women 27-45 years of age); 1210 received at least one dose of 9vHPV vaccine. Anti-HPV 16/18/31/33/45/52/58 responses in adult women were non-inferior to young women at Month 7. Across these 7 HPV types, the GMT ratios ranged from 0.66-0.73; the lower bound of the 95% confidence interval of the GMT ratio ranged from 0.60-0.67. The non-inferiority criterion was met since the lower bound of the GMT ratios was >0.50 for each of the 7 HPV types. Seroconversion for each of the 9 HPV types was >99% in both age groups. The proportion of participants with injection-site AEs was similar in the older and younger age groups (85.5% vs. 87.9%, respectively). The proportion of participants with vaccine-related systemic AEs was also similar in the older and younger age groups (24.1% vs. 25.1%, respectively). No participants died during the study and there were no vaccine-related serious AEs; one participant discontinued from vaccination due to an AE that was not vaccine-related.

Conclusions: The 9vHPV vaccine regimen was highly immunogenic in women 16-45 years of age, resulting in non-inferior anti-HPV GMTs for HPV types 16/18/31/33/45/52/58 in women 27-45 years of age compared with women 16-26 years of age, and the 9vHPV vaccine was generally well tolerated in both age groups.

#0443

5 - HPV prophylactic vaccines

Natural boosting occurs in HPV vaccinated adolescents; exposure, immune response or both?

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Background/Objectives: Immune responses after HPV exposure in vaccinated individuals might enhance ("boost') vaccine-induced immunity. A previous study of one- and two-dose recipients of the quadrivalent HPV vaccine (QHPV), indicated that the antibody levels at 48 months were constant or higher than those at 36 months. We aimed to evaluate whether natural boosting occurs and the associated factors up to 10 years post-vaccination in young women who received two or three doses of QHPV.

Methods: Girls aged 9-13 years were randomized to receive two or three doses of QHPV. Blood samples were collected before and at 7, 24, 60 and 120 months post-first dose and surveys were taken at baseline and each year between 60 and 120 months. Antibodies were measured by the competitive Luminex (cLIA) and total IgG (tIgG) Luminex immunoassays. A boosting event was defined as an increase in antibodies at any time point after the 7 month sample collection above the assay variability threshold without interval immunization. A generalized estimating equations (GEE) model with an unstructured correlation matrix was used to examine an association between antibody titres, socio-demographics, sexual behavior and HPV exposure over time.

Results: Of 73 participants who completed blood sampling at all time points, 17 (23.3%) showed at least one boosting event for HPV6, 11, 16 or 18 during follow-up by cLIA. Those with higher antibody titres at any time point during follow-up had significantly lower odds for an increase in antibodies in the period thereafter (HPV6 0.06 (95%CI 0.02-0.16), HPV11 0.41 (95%CI 0.33-0.53), HPV16 0.24 (95%CI 0.09-0.66), HPV18 0.42 (95%CI 0.28-0.63)). Geometric mean titres between two and three dose recipients were not significantly different, but two-dose recipients were more likely to show a boosting event during follow-up OR 3.44 (95%CI 1.07-11.11). Eight participants (11%) showed a boosting event measured by tIgG. All of these events occurred between 60 and 120 months post-vaccination. Evaluation of HPV DNA status in relation to increasing antibody titres is underway.

Conclusions: This study showed increasing antibody titres in 23% of adolescents vaccinated with QHPV during 10 years post-vaccination follow-up. An association with boosting was found for those with lower initial antibody titres and for participants receiving a two-dose schedule. The increase in antibody titres could reflect a response to natural exposure or maturation of the immune response.

#0351

5 - HPV prophylactic vaccines

COMPARATIVE STUDY EVALUATING PATIENTS DECISION MAKING BETWEEN HPV4 VS HPV9 VACCINE APPLICATION IN MEXICO

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Background/Objectives: Genital HPV is a very common virus that is passed through direct skin-to-skin contact during sexual activity. Most sexually active people will get HPV at some time in their lives. There are more than 40 types of HPV that can infect the genital areas, most HPV types cause no symptoms and go away on their own. But some types can cause cancer in both women and men, such as cervical, vulvar, vaginal, anal, head and neck, penile and some skin cancers. Other types of HPV can cause warts in the genital areas of men and women. Every year, about 12,000 women are diagnosed with cervical cancer and 4,000 women die from this disease in the U.S. About 1% of sexually active adults in the U.S. have visible genital warts at any point in time. Ideally they should get the vaccine before they become sexually active and exposed to HPV. Perception towards HPV vaccination is a key factor in achieving good coverage and is linked to proper education and knowledge about the disease. Vaccination in sexually active people may also be benefitial, but maybe to a lesser degree because of exposition to one or more of the HPV types targeted by the vaccines. Few sexually active young women and men are infected with all HPV types prevented by the vaccines, so most young adults could still get protected by the vaccine.

Methods: We conducted a comparative and prospective study of 54 patients out of 242 data base from 8/2018 to 8/2019 at IMIGO (Mexican Institute of Infectious Diseases in Obstetrics and Gynecology) Monterrey MEXICO, ages 9 to 45 years to assess their decision making when deciding to get vaccinated against HPV between HPV4 and HPV9 vaccines using an electronic survey. All patients received basic standarized comparative document between HPV4 and HPV9. Inclusion criteria: receiving either HPV vaccine, having a complete scheme or partial, having a previous HPV4 partial or complete vaccine scheme, having purchased HPV vaccines, aleatory and voluntary invitation to participate in the survey. Exclusion criteria: not willing to participate in the survey

Results: Among the parameters evaluated, when asking about why the vaccine was applied, main responses were due to positive previous HPV detection test and by medical recommendation. Of the interviewed patients only 2/3 referred complete vaccination schedules, 33% HPV9 and 38% HPV4, rest of the patients had an incomplete scheme 69% reported it in progress. Patients who decided to receive the HPV9 vaccine 61% was by medical recommendation, 72% was by the amount of virus included in the vaccine, 64% said the price of the vaccine was not an issue in deciding between both vaccines. Another aspect evaluated was if HPV4 dose or doses had already been applied and patients opted to receive HPV9 50%, from this particular group 88% said they felt more protected than before. Regarding adverse effects, 86% reported none, as pain in site of injection, headache and fatigue accounted 4.6% each respectively. Perception of patients was the majority considered that the HPV9 to be safer (56.25%), more effective(37.5%), more protective (62.5%), and more necessary(37.5%) than HPV4.

Conclusions: Previous HPV infection and physician recommendation to vaccinate are the main drivers to get patients vaccinated against HPV according to our results. we also found that perception towards HPV9 vaccine is positive and patients feel safer with this vaccine. The shifting fenomenon from HPV4 to HPV9 is also particularly driven by the pursuit of a better protection against HPV.

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#0343

5 - HPV prophylactic vaccines

HPV VACCINATION UPTAKE IN BOYS AFTER INTRODUCTION OF GENDER-NEUTRAL HPV VACCINATION IN GERMANY - A RETROSPECTIVE DATABASE ANALYSIS (IMS VACCINE ANALYZER)

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Background/Objectives: HPV vaccination has been recommended in Germany for girls since 2007. In June 2018 the German Standing Committee on Vaccination (STIKO) published its first gender-neutral recommendation for HPV vaccination for all girls and boys 9-14 years old (with catch up to 17). Since January 2019 gender-neutral HPV vaccination is part of mandatory funding by statutory health insurances in all country regions for individuals 9 to 17 years old. Vaccination is provided by office-based physicians and no general invitation or reminder system exists in Germany. The aim of this study was to monitor the monthly uptake and implementation dynamics of HPV vaccination in boys in Germany.

Methods: The study design consisted of a retrospective database analysis between January 2018 and April 2019. The used IMS Vaccine Analyzer is a database with anonymized digital medical vaccination records from a panel of approximately 350 office-based physicians (pediatricians, GP, gynecologists). Numbers documented in the IMS Vaccine Analyzer database were projected to national level by using a separate database, IMS Pharmascope Vaccines, which contains 100% of vaccinations distributed in Germany. The primary outcome of the study was the monthly number of boys receiving the first dose of HPV vaccination, stratified by doctor's specialty, and patient's age. Secondary outcomes included the monthly number of vaccinated girls. No data on population size existed for the presented analyses.

Results: While the monthly number of boys 9 to 17 years old receiving HPV vaccination in Germany before the gender-neutral STIKO recommendation was low (first doses 98 to 950 per month January 2018 to May 2018), it started to steadily increase from a low level in June 2018 (832) to December 2018 (9,670) and further increased sharply by almost 200% with fully implemented reimbursement in January 2019 (28,691). A further steady increase was observed until April 2019 (51,934). Most vaccinated boys were 13 or 14 years old (16% in April 2019) and most vaccinations were given by pediatricians (75%). The monthly number of girls 9 to 17 years old receiving first dose of HPV vaccination during the observation period fluctuated between 27,287 and 50,788.

Conclusions: The results demonstrate a strong increase in the number of boys that received HPV vaccination in Germany after publication of the gender-neutral recommendation in June 2018 and full reimbursement by statutory health insurances in January 2019. The monthly number of boys receiving the first dose reached the level of girls. Further analyses will link the results to population size to estimate HPV vaccination coverage in boys in Germany.

#0396

5 - HPV prophylactic vaccines

POPULATION-BASED HPV SEROSURVEY AMONG UNVACCINATED FEMALES REVEALS HPV16 HERD EFFECT POST- GENDER-NEUTRAL VACCINATION WITH MODERATE VACCINATION COVERAGE: FOLLOW-UP OF A COMMUNITY RANDOMISED TRIAL

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Background/Objectives: The elimination of cervical cancer through means of human papillomavirus (HPV) vaccination programs requires the attainment of herd effect. For HPV16, which has a high basic reproduction number, the vaccination coverage required to achieve herd effect has been suggested to exceed that realistically achieved in average populations. We evaluated which vaccination strategy provides the best herd effect when vaccination coverage is moderate.

Methods: A population-based community randomised HPV vaccination trial was launched between 2007-10. 33 communities were randomised to receive moderate vaccination coverage gender-neutral, girls only, or no HPV vaccination of 1992-95 born early adolescents. We retrieved samples biobanked during 2005-16 (from the era preceding completion of vaccination, 2005-10, and the post-vaccination era, 2011-16) from all 8022 unvaccinated pregnant women ≤23 years old were resident in the 33 communities. The retrieved serum samples were analysed for antibodies to 17 HPV types and herpes simplex virus type 2 (HSV-2) using Luminex assays. To measure herd effects, pre-vaccination era HPV seroprevalence was compared to that post-vaccination, by trial arm, applying stratification of age and core-group membership.

Results: A slight post-vaccination reduction in HPV18 seroprevalence occurred in both the girls only and gender-neutral intervention arms. However, significant reduction in HPV16 seropositivity was only observed in the gender-neutral arm (PR=0.79, 0.72-0.87) and amplified further among the HSV-2 seropositives (PRHSV2+=0.64, 0.50-0.81).

Conclusions: The implementation of gender-neutral vaccination when vaccination coverage is only moderate enables herd effect against HPV16, the most difficult HPV type to eliminate.

FC 03 - Epidemiology and natural history - I

#0088

2 - Epidemiology and natural history

Human Papillomavirus types in cervical dysplasia among young HPV-vaccinated women: Population-based nested case-control study

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Background/Objectives: HPV vaccines protect against infections with the most oncogenic HPV types, cervical intraepithelial neoplasia (CIN) and cervical cancer. We investigated if CIN lesions developing in HPV-vaccinated women are associated with vaccine-targeted HPV types or not.

Methods: Linkage of the Swedish vaccination and cervical screening registries identified all females born 1980-2000 who had been HPV vaccinated before 2014-12-31 (n=305320) and had attended cervical screening in 2006-2018 (N=79,491). We further selected women HPV vaccinated below 17 years of age and screened in the greater Stockholm region (N=5,332). Among those, 125 developed CIN 1-3 and had their cervical sampleavailable. After 1:2 matching to disease free controls (N=242), the cryopreserved samples were analyzed for HPV DNA and associations between HPV DNA type and CIN diagnosis were estimated with conditional logistic regression.

Results: Vaccine-targeted HPV types were rare among both CIN1-3 cases (2.4% HPV16, 0.8% HPV18) and their matched controls (0.4% HPV16 and 18). No women had HPV6 or 11. The CIN lesions were associated with the non-vaccine HPV types 31, 33, 42, 45, 51, 52, 56, 59 and 66.

Conclusions: CIN lesions among young HPV vaccinated women are mostly attributable to infection with non-vaccine HPV types. The phenomenon may be of importance for surveillance and design of cervical cancer control strategies.

#0420

9 - HPV screening

Co-infections of HPV16/18 with other high-risk HPV types and the risk of cervical carcinogenesis: a large population-based study

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Background/Objectives: Human papillomavirus (HPV) 16/18 genotyping is considered to be an effective way for triage of high-risk (hr) HPV-positive women in primary hr-HPV screening for cervical cancer. Approximately 20.4-56.3% of HPV infected women are simultaneously infected with more than one HPV type. However, the effect of HPV co-infection has been controversial. The study aims to evaluate whether co-infected with other hr-HPV types will affect the risk of cervical carcinogenesis in HPV16/18 positive women.

Methods: A total of 313,704 women ≥30 years were screened during the study period. Our cervical cancer screening process was designed according to SGO/ASCCP recommended, which used hr-HPV genotyping as first-line primary screening for cervical cancer [1]. Among them, 4933 HPV16/18-positive subjects underwent colposcopy-directed biopsy. HPV genotypes were identified using the cobas4800 hr-HPV genotyping system, which could detect 14 hr-HPV types including HPV16, HPV18, and "other hr-HPV" types (HPV31/33/35/39/45/51/52/56/58/59/66/68). Multinomial logistic regression was used to model different HPV16/18 infected patterns.

Results: The overall prevalence rates of hr-HPV and HPV16/18 were 7.85% (24,456/311,382) and 1.95% (6086/311,382) respectively. Among HPV16/18 positive individuals, 33.24% (2023/6086) were co-infected with other hr-HPVs. Of the 4933 women who underwent colposcopy, their HPV16/18 infected patterns were as follows: 52.38% (2584/4933) HVP16 only, 23.54% (1161/4933) HPV16+other hr-HPVs, 14.98% (739/4933) HPV18 only, 6.83 %(337/4933) HPV18+other hr-HPVs, 1.13% (56/4933) HPV16+18, 1.13% (56/4933) HPV16+18+other hr-HPVs. We also found five epidemiological factors (education, post-coital bleeding, menopause, the family history of cancer, and vaginal cleanliness) that may affect the progression of cervical carcinogenesis. After adjusting these cofactors, compared with single HPV16 infection, the risk of developing cervical intraepithelial neoplasia (CIN) grade 3 or greater (CIN3+) was significantly lower in HPV16+other hr-HPVs group ([OR]=0.637, 95%[CI]=0.493 - 0.822).However, no significant difference was showed between HPV16 only infection with HPV16+HPV18 or HPV16+HPV18+other hr-HPVs infection in either CIN2 versus <CIN2 or CIN3+ versus <CIN2. When focusing on HPV18 infections, HPV16+18 and HPV16+18+other hr-HPVs positive women were found to have a higher risk of CIN2 than single HPV18 infected patients ([OR]=4.822, 95% [CI]=1.676 - 13.872; [OR]=5.559, 95% [CI]=1.924 - 16.060 respectively).

Conclusions: To our knowledge, this papulation based study has one of the largest sample sizes of HPV16 /18 positive women with corresponding histologic results. We found that HPV16/18 co-infected with other hr-HPVs is a common phenomenon. We also demonstrated that the single HPV16 infection carries a higher risk for the progression to CIN3+ compared to simultaneous infections of HPV 16 and other hr-HPVs (excluding HPV18). However, the risk of developing CIN2 in HPV18 positive patients co-infected with HPV16 was higher than that patients with single HPV18 infection. Overall, our study may potentially provide evidence of risk stratification within different HPV16/18 infected patterns.

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#0152

2 - Epidemiology and natural history

HPV - associated cancers in Russia

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Background/Objectives: In the former Soviet Union cytological testing for early detection of cervical cancer was obligatory. Although this mass application of diagnostic test could hardly be referred to as the population-based quality controled screening in 1970-1985 its coverage of women of reproductive age was substantial. After the breakup of the USSR the existing practice of preventive check-ups was abandoned. Although there were some attempts to introduce HPV-vaccination in a few regions of Russia, HPV vaccination is still not included in the national vaccination calendar. The analyses of incidence and mortality time trends of cancer of the cervix and other HPV-associated cancers

Methods: Incidence cases and new deaths were obtained from the cancer statistics database of the P.A. Herzen Moscow Cancer Institute and stratified by cancer type, year of diagnosis, sex, 5-year and 10-year age groups. Incidence rates were available from 1980 to 2017 and mortality rates from 1965 to 2017. Age-standardized incidence and mortality rates (ASR) per 100, 000 population were estimated using the world standard population. To graphically present the direction of the trends, regression curves were fitted to provide smoothed lines through the scatterplot of ASR by calendar periods. We carried out a joinpoint regression analysis of incidence and mortality trends and projected them for 2030. We further examined mortality trends for cervical cancer by birth cohort and age.

Results: Cervical cancer incidence and mortality in Russia are high relative to other countries of Europe. Incidence and mortality of cancer of the cervix substantially decreased from 1970 to 1993. The turnover of the trend occurred in 1993-1995 and since then the incidence has been increasing while mortality rates have leveled. It is projected that the age-standardized incidence rates of cervical cancer will continue to increase from 15 in 2016 to 20 per 100,000 population in 2030 and that there will be 28 new cases of cervical cancer per 100, 000 population in 2030. Although mortality for all ages seems stable, it is projected that age-specific mortality in women aged 50 years and older will increase approximately by 60%. Incidence of other cancers associated with HPV in Russia is low. However it is also projected to increase.

Conclusions: The high cervical cancer burden in Russia is exacerbated by a lack of population-based screening. Incidence and mortality of cervical cancer and other HPV-associated cancers are bound to increase if the Russian health authorities will further ignore the evidence of effectiveness of HPV vaccination and HPV testing for screening of cervical cancer.

#0231

2 - Epidemiology and natural history

HPV PREVALENCE AND TYPE IN WOMEN ATTENDING CERVICAL CANCER SCREENING IN SIKASSO, MALI: A CROSS-SECTIONAL STUDY

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Background/Objectives: In Mali, about 2206 women are newly diagnosed with cervical cancer however data is not yet available on the HPV burden in general population of Mali. In Western Africa, studies reported that about 4.3% of women in the general population harbored cervical HPV-16/18 infection and 55.6% of cervical cancer are attributed to HPV 16 or 18. We performed a cross-sectional study in a population of women who have been screened for cervical cancer in CERKES clinical care center in Sikasso, Mali, to assess HPV prevalence and associated cervical lesions and risk factors associated with.

Methods: Women who attended for cervical cancer screening by visual inspection with acid acetic (VIA) or Lugol's iodine (VILI) were included and liquid-based cytology was collected for each one. Socio-demographic data including age, marital status, education level, contraception and medical data including presence of lesions or HIV status were collected. HPV-testing was performed with the AnyplexII HPV28 (Seegene) which allowed the detection of 19 high-risk HPV (hrHPV) and 9 low-risk HPV (lrHPV). GraphPad software was used to perform Fisher t and Mann-Whitney U test.

Results: Overall, 144 women were included with a median [IQR] age of 37 [29-44] years. A majority were married (78%) with a marital median age of 19 [17-22] years. Forty-one (35%) were polygamous and 111 (77%) did not use contraception. A total of 113 reached primary school or less and 44 (31%) were HIV-infected. Overall, all HPV types, hrHPV and lrHPV prevalence was 75%, 69% and 26% respectively with a median [IQR] of 2 [0.75-4], 1[0-3] and 0 [0-1] different HPV respectively. Among hrHPV, HPV31 was the most prevalent (27.8%), followed by HPV56 (25%) and HPV82 (21.5%). Among lrHPV, HPV42 was the most prevalent (11%), followed by HPV6 (7%) and HPV54 (6.3%). HPV16 and HPV18 prevalence was respectively 9.7% and 7.6%. Among parameters analyzed, prevalence of hrHPV was significantly higher in HIV-infected women than that HIV-uninfected (84% vs 61%, p=0.0074) (Table 1) and with significantly higher hrHPV multi-infection (81% vs 58%, p=0.02). The 20 patients (of whom 4 HIV+) with positive VIA/VILI screening at the time of HPV sampling had cervical biopsy. Among them, 6 had cervical intraepithelial neoplasia grade 1 (CIN1, of whom 1 HIV+) and 5 CIN2 (all HIV-). Seven of the 11 patients with cervical lesion were hrHPV positive and HPV16 was involved in only one case. Multi-infections by others hrHPV occurred in 4/7 cases.

Conclusions: Cervical lesions was low in our population (7.5%), whereas hrHPV prevalence was high (69%) and significantly higher among HIV-infected women, as previously reported. However, HPV16 was not the most prevalent in both cervical infection and cervical lesion.

#0412

9 - HPV screening

Multiple HPV genital infection in unvaccinated young population from Brazil: a cross-sectional study

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Background/Objectives: Genital human papillomavirus (HPV) infection with more than one type is common, especially in young people. Understanding the characteristics of multiple HPV infections is critical in the era of multivalent vaccine. The aim of the present study was to estimate the prevalence of multiple HPV infection and the most common virus types in young adults who use the Public Health System in Brazil.

Methods: A cross-sectional, nationwide, multicentre study with sexually active young adults (16-25 years old) were enrolled in 119 primary healthcare centres throughout all 27 capitals of the country between September 2016 and November 2017. Participants vaccinated against HPV were excluded from analysis. Samples (cervical and penile specimens) were extracted by using the automated MagnaPure platform. Roche Linear Array® was performed for HPV detection in a central lab. The test detects 37 types of HPV simultaneously. Young adults infected with more than one HPV type were considered to have multiple infections. To adjust the distribution of the sample to the study population, we weighted the measures by size of population in each capital.

Results: From 6,388 participants, 30.97% (95% CI 29.00 - 32.95) had multiple infection. At least one type of high-risk HPV was present in 81.40% of all multiple infections. Among participants with HPV, each overall type was detected more frequently in association with other types than alone. Multiple infection was more commonly found in women than men (33.00% vs. 27.45%, $p = 0.023$), and in participants under 22 years (34.80% vs. 26.60%, $p < 0.001$). Single participants (36.92%), with more than two sexual partners at last year (40.54%), and previous sexually transmitted disease (43.45%) had higher rates of multiple infection.

Conclusions: The prevalence of multiple HPV infection was substantially high in this population. However, its impact remains unclear when compared to single infection on the role of cervical cancer development, which should be further investigated.

#0014

2 - Epidemiology and natural history

Risk of acquiring human papillomavirus DNA for occupational surgical smoke exposure in gynecologists in China.

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Background/Objectives: This study aimed to investigate whether gynecologists who had done with electrosurgery including loop electrosurgical excision procedure (LEEP) were at risk of acquiring human papillomavirus (HPV) through the surgical smoke

Methods: The related questionnaire was designed and 700 cases of gynecologists' nasal swabs samples were collected in 67 hospitals from Zhejiang, China. Meanwhile, flow fluorescence hybridization technique was used to detect HPV infection, and Chi-square test was applied to analyze whether electrical operation was in correlation with HPV infection in surgeons' nose.

Results: The HPV infection rate in the participants operating electrosurgery (8.96%, 42/469) or LEEP (10.11%, 36/356) was significantly higher than the remaining participants without electrosurgery (1.73%, 4/231) or LEEP (2.91%, 10/344), respectively. The most prevalent HPV genotype in electrosurgery group was HPV16 (76.19%, 32/42). The HPV positive rate was increasing in the group who had the longer electrical surgery times with electrosurgery (P =0.016). Meanwhile, the HPV detection rate was significantly lower in electrosurgery operators who had surgical mask (7.64%, 33/432) than the ones who did not use protection mask (24.32%, 9/37). Furthermore, N95 mask (0%, 0/196) obviously reduced the risk for HPV infection than general mask (13.98%, 33/236, P)

Conclusions: Gynecologists who had done with electrosurgery including LEEP were at risk of acquiring HPV. Surgical smoke, especially N95 mask, could significantly decrease the hazard of transmission of HPV from surgical smoke. Future studies were urgently warranted to demonstrate whether HPV virus from surgical smoke during LEEP was viable even pathogenic to operators.Keywords: Electrosurgery, HPV, surgical smoke

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#0056

2 - Epidemiology and natural history

ASSOCIATION OF AGE AND VIRAL FACTORS WITH HIGH-RISK HPV PERSISTENCE: A RETROSPECTIVE FOLLOW-UP STUDY

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Background/Objectives: Cervical HR-HPV persistence is the main risk factor for cervical cancer. We aim to investigate the association of age and viral factors with HR-HPV persistence. In this study, the time-dependent variable was introduced to answer two intriguing questions: "How does the risk change with time?", and "When would the risk change qualitatively if such time points exist? "

Methods: We launched a large-scale, retrospective follow-up study employing a natural population design (which enabled us to keep track of half a million HPV tests). From 2010 to 2017, we recorded 343 128 women contributing 390 411 Cervista HR-HPV tests (Data C3) and 157 123 women contributing 206 505 GenoArray HR-HPV tests (Data G14) from nine medical centers in central and eastern China. We collapsed the test results and identified 9234 HPV-specific baseline-negative records for time-to-event analyses. The study event was defined as HPV clearance. Therefore, hazard ratio (HR) < 1 indicated a higher risk of HPV persistence, which is opposite to the common meaning of HR.

Results: The median persistence time was 375 and 541.5 days for Data C3 and Data G14. Age, HR-HPV group/type, coinfection, and recurrence of infection were identified as risk factors for HR-HPV persistence. So far, most traditional studies just reported an overall (i.e., not time-dependent) hazard ratio for age, coinfection and recurrent infection etc. An overall hazard ratio implies the risk to be constant from the beginning to the end of infections. However, our data suggested that their risk changed over time. For every 5-year increase in age, a 15% (95% confidence interval [CI], 11%-19%) decrease in clearance rate was observed only after 400 days of infection. For each additional co-infected HPV, the HR was 1.80 (95% CI, 1.63-1.97) on infection initiation, but decreased by 22% (95% CI, 18%-26%) every 100 days. The HR of infection recurrence was 0.48 (95% CI, 0.32-0.72). The findings were consistent across different populations and test methods and were robust in sensitivity analysis.

Conclusions: We found a time-dependent association of age and viral factors with HPV clearance. Older age reduced HPV clearance only after 400 days of infection. Coinfection promoted HPV clearance in the beginning, but the effect attenuated and reversed as infection persisted. Recurrent same-type infections cleared slower than the previous one.

FC 04 - Epidemiology and natural history II

#0532

39 - Fertility and HPV

Two distinct HPV mechanisms cause spontaneous miscarriage

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Background/Objectives: Despite being one of the most prevalent sexually transmitted viral infection in both men and women worldwide, Human Papillomavirus (HPV) infection was only recently and in scarce studies linked to reduced fertility outcomes1. One of the major reasons why it took so long to realize infectious HPV virions impair fertility is because we often failed to see the different impact of infection and disease, HPV viruses and HPV virions2. On one hand HPV can cause the well-known but rather uncommon transformation of HPV infected dividing cells into cancer on the uterine cervix or other organs. These HPV morphotypes are incorporated into the cell's DNA and are no longer infectious3. On the other hand, the more frequent free infectious HPV virions can bind the spermatozoa's head4, induce sperm DNA damage, causing temporal subfertility demonstrated by reduced clinical pregnancy rates in subfertile women receiving inseminations with HPV positive semen1. Additionally, in vitro experiments have demonstrated that spermatozoa can not only transfer HPV virions4 to the oocyte, but the transferred HPV virions also induce stage-specific maturation arrest in infected embryos5. It is clear that in cervical HPV infection during pregnancy both the virion producing and clonal transforming pathways are involved2. Whereas premature rupture of the membranes, spontaneous preterm labor, pre-eclampsia, and placental "villitis' not otherwise specified is probably a burden due to the virion producing pathway, the higher incidence of spontaneous abortions might be ascribed to the division stop induced by the presence of HPV oncogenes of the transforming pathway6. We aimed to determine the impact of each of the HPV induced pathways (infectious/transforming) on spontaneous miscarriage.

Methods: Immunohistochemistry for HPV L1 viral capsid was used to identify HPV in the aborted tissue of 133 women who had spontaneous miscarriage, p16 staining was used to locate HPV staining in dividing and non-dividing cells.

Results: HPV L1 positivity was observed in 63.9% of tissue of spontaneous miscarriage (85/133). In all HPV L1 negative cases the p16 staining was negative. For the HPV L1+ cases, 58.5% was p16 positive (dividing cells, transforming) and 41.5% was p16 negative (non-dividing cells, infectious). The HPV L1+/p16+ cases miscarried in average after 9 weeks and the HPV L1+/p16- two weeks earlier in average after 7 weeks (p=0.0003).

Conclusions: In almost 2/3rd of spontaneous miscarriages HPV could be detected. Infectious virion induced miscarriage occurred in average 2 weeks earlier than when the HPV transforming pathway induced embryo division arrest.

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#0107

3 - Pathogenesis

ASSOCIATION OF IL4R I75V POLYMORPHISM WITH SUSCPEPTIBILITY TO HPV INFECTION, CERVICAL LESION AND CERVICAL CANCER AMONG WOMEN LIVING IN REPUBLIC NORTH MACEDONIA

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Background/Objectives: Human Papillomavirus (HPV) infection is strongly associated with squamous intraepithelial lesions (SIL) and cervical cancer (CCa) developement. The clearance of HPV is affected by cytokines that have very important role in defence from viral infections as well as in immune response modulation during carcinogenesis. Polymorphism in these genes could influence HPV and cervical lesion susceptibility. Here we analyzed weather IL4R I75V polymorphism is associated with HPV positive SILs and CCa in women living in R North Macedonia.

Methods: We analyzed 113 healthy, HPV and cytolocicaly negative women and 134 HPV positive cases stratified in three groups: LSIL (n=40), HSIL/CCa (n=94) and group consisted of all cases (LSIL/HSIL/CCa)(n=134). HPV detection was performed using real time PCR commertcial tests and IL4R genotyping was done using SNapShot analysis.

Results: Comparasion of allele and genotype distribution between cases and controls didn't show statisticaly difference between each groups. There are no significant relation between IL4R I75V polymorphism in HPV positive HSIL/CCa compred to control group (p=0.4) as well as in all cases compred to controls (p=0.9), but we find that AA genotype has significaly lower frequency in LSIL (25%) compared to HSIL/CCa group (30.0%), (p=0.03, OR=0.4; 95%CI 0.14-1.1).

Conclusions: We demostrated that GG genotype of IL4RI75V could give protection against progresion of HPV positive LSIL to HSL or CCa in women living in R Nort Macedonia.

#0459

2 - Epidemiology and natural history

Incidence and trends of HPV-associated cancers in men in the United States

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Background/Objectives: HPV is estimated to cause 5% of all cancers, in which HPV 16 is the most common genotype. However, screening is not available for most of the HPV-associated cancers in men, and most of these cancers have been increasing in prevalence. We aim to determine the incidence of anal, oropharyngeal, and penile cancers among men in the United States and to describe the regional and socioeconomic variation.

Methods: We collected data from the US Cancer Statistics registry, which covers 97% of the population and calculated adjusted incidence rates. For oropharyngeal cancers, we combined both oropharynx and tonsil subsites. We assessed annual trends among sociodemographic and geographic subgroups using joinpoint analysis.

Results: We did not find any joinpoints in any of the HPV-associated cancers (Figure 1). Both anal and oropharyngeal cancers have been increasing (APC: 1.59 and 3.05, respectively) while penile cancer has remained rather consistent (APC: 0.05). In 2015, oropharyngeal cancer is had the highest age-adjusted incidence per 100,000 at 4.62 (95% confidence interval (CI): 4.52-4.72) followed by anal cancer (1.48, 95% CI: 1.42-1.54)) and lastly penile cancer (0.82, 95% CI: 0.78-0.87). There are significant differences in incidence and APC by race for anal and oropharyngeal cancer. For anal cancer, incidence rates are much higher in Black Americans (2015 incidence rate 1.94 (95% CI: 1.74-2.16) per 100,000) compared with White Americans (2015 incidence rate 1.46 (95% CI: 1.40-1.52) per 100,000). For oropharyngeal cancer, incidence increased among White Americans (APC: 3.64) from 2000 to 2015 but decreased among Black Americans (APC: -0.72), resulting in higher 2015 incidence rates among White Americans (4.98 (95% CI: 4.86-5.09) per 100,000) than Black Americans (3.56 (95% CI: 3.29-3.85) per 100,000). There is significant heterogeneity among the incidence rates and APC within regions of the United States. Anal cancer incidence is increasing among all regions except the "West Region" where rates are steady. In oropharyngeal cancer, rates are rising across all regions with the Midwest having the highest rate of increase and south have the highest incidences. For penile cancer, rates are the lowest in the South, while the other regions are somewhat consistent.

Conclusions: Anal and oropharyngeal cancer rates are increasing in men, while penile cancer has remained mostly consistent. The increase in the incidence rates of oropharyngeal cancer is almost entirely in White Americans due to the role of HPV and changing sexual practices compounded with the decreasing smoking rates. Similarly, the rise in anal cancer is also likely due to HPV and changing sexual practices. However, the increasing rate among Black men is possibly due to HIV since it disproportionately affects Black men who have sex with men. Interestingly, rates in the "West" region of the United States has remained constant, which could be due to the adoption of screening and decreasing HIV rates.

Figure 1

#0077

2 - Epidemiology and natural history

LONG-TERM IMPACT OF SCREENING ON CERVICAL CANCER EPIDEMIOLOGY: CHANGING SURVIVORSHIP

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Background/Objectives: Before the introduction of cytology screening in the 1970s, cervical cancer (CC) was the 4th most common female cancer, and the most common cancer in women 25-39 years of age in Norway. After half a century, in 2016, CC is the 11th most common cancer among women overall, and 3rd most common among younger women. This change reflects the impact of screening which has an aim to reduce CC incidence and mortality by detecting and treating pre-cancers. Less is known about the effect of screening on CC patient profile and survivorship. With treatments including hysterectomy combined with radiotherapy and chemotherapy, 80-90% of CC patients with Stage I-II, and 60% of patients with Stage III can be cured. However, treatment often causes unwanted side effects including physical changes, menopausal symptoms, infertility, and sexual dysfunction. The effect of screening on cancer stage and patient age affect survivorship and risk of having secondary cancers. Currently there are few available studies related to the epidemiology of CC survivors. Our aim was to describe the long-term changes in incidence, prevalence, mortality and survival of CC in Norway and assess risk of secondary cancers among CC patients.

Methods: All cervical cancer cases diagnosed during the period of 1953 to 2018 were identified from the Cancer Registry of Norway. The age standardized incidence and mortality rates (ASIR), age-specific IR, and prevalence, were calculated with corresponding trends. Five-year relative survival and long-term risk of secondary cancers will also be assessed. Trend tests for the change in prevalence, relative survival and subsequent cancer risk will be performed.

Results: During the period of 1953 to 1974, the annual ASIR of CC increased from 14.5/105 to 21.1/105, and decreased significantly thereafter to 10.3/105 in 2016. Mortality from cervical cancer decreased from 7.4/105 in 1953 to 2.0/105 in 2016. Compared to the period of 1970-1974, the ASIR of cervical cancer was 1.9 times lower in the period of 2012-2016. Most of the cancer patients were 35-39 years old in 2012-2016, while in 1970-1974, the cancer patients were mostly 45-54 years of age. In total, the number of women in Norway living with a CC diagnosis increased from 4513 in 1974 to 7283 in 2016.

Conclusions: Cervical cancer screening has changed the epidemiological profile of cervical cancer patients in Norway. The typical cancer patient is now younger with prolonged survival, resulting in an increased number of women living with CC. Research focusing on the long-term effects of cancer treatment and quality of life among cervical cancer survivors is needed.

#0052

2 - Epidemiology and natural history

THE ASSOCIATION BETWEEN DIETARY FOLATE AND VITAMIN B12 INTAKE AND THE ACQUISITION OF GENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTION

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Background/Objectives: To examine the association between dietary folate and vitamin B12 intake and the acquisition of genotype specific HPV infection.

Methods: Secondary data analysis was conducted using data derived from the Hawaï HPV male longitudinal study. At baseline, dietary intake was determined by a quantitative food frequency questionnaire (QFFQ). HPV testing and genotyping were conducted on genital swabbings collected at baseline and follow-up visits. Recurrent events survival analysis was conducted.

Results: A total of 318 men, who completed QFFQ and had at least 2 follow-up visits, were eligible. Their mean age (standard deviation) was 27.7 (11.0) years. Among all men, 566 incident genotype specific HPVs were acquired. The proportion of oncogenic HPVs (45.8%, 259/566) was slightly lower than non-oncogenic HPVs (54.2%, 307/566). Multivariable models were adjusted for age, number of lifetime female sexual partners, condoms use, and hepatitis C virus infection referenced the highest tertile of dietary intake. Men whose dietary folate intake was in the second tertile had a higher risk of acquiring oncogenic HPV: adjusted HR 1.16, 95% CI 0.80-1.69. Men whose dietary vitamin B12 was in the second tertile had a higher risk of acquiring non-oncogenic HPV: HR 1.47, 95% CI 1.01-2.12.

Conclusions: Consuming a diet rich in vitamin B12 might be associated with a lower risk of acquiring HPVs. As HPV is sexually transmitted between individuals, further studies on the role of dietary intake and HPVs are needed to identify public health interventions to reduce the burden of HPV-related diseases in both men and women.

#0070

2 - Epidemiology and natural history

Projected cervical Cancer incidence in Swaziland using three methods and local survey estimates

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Background/Objectives: The scarcity of country data (e.g. a cancer registry) for the burden of cervical cancer (CC) in low-income countries (LCIs) such as Swaziland remains a huge challenge. Such data are critical to inform local decision-making regarding resource allocation [1]. We aimed to estimate likely cervical cancer incidence in Swaziland using three different methodologies (triangulation), to help better inform local policy guidance regarding likely higher "true" burden and increased resource allocation required for treatment, cervical cancer screening and HPV vaccine implementation.

Methods: Three methods were applied to estimate CC incidence, namely: 1) application of age-specific CC incidence rates for Southern African region from GLOBOCAN 2012 extrapolated to the 2014 Swaziland female population; 2) a linear regression based model with transformed age-standardised CC incidence against hr-HPV (with and without HIV as a covariate) prevalence among women with normal cervical cytology; and 3) a mathematical model, using a natural history approach based on parameter estimates from various available literature and local survey estimates. We then triangulated estimates and uncertainty from the three models to estimate the most likely CC incidence rate for Swaziland in 2015.

Results: The projected incidence estimates for models 1-3 were 69.4 (95% CI: 66.7-72.1), 62.6 per 100,000 (95%CI: 53.7-71.8) and 44.6 per 100,000 (41.5 to 52.1) respectively. Model 2 with HIV prevalence as covariate estimated a higher CC incidence rate estimate of 101.1 per 100,000 (95%CI: 90.3-112.2). The triangulated ("averaged') age-standardized CC incidence based across the 3 models for 2015 was estimated at 69.4 per 100,000 (95% CI: 63.0-77.1) in Swaziland.

Conclusions: It is widely accepted that cancer incidence (and in this case CC) is underestimated in settings with poor and lacking registry data. Our findings suggest that the projected burden of CC is higher than that suggested from other sources. Local health policy decisions and decision-makers need to re-assess resource allocation to prevent and treat CC effectively, which is likely to persist given the very high burden of hr-HPV within the country.

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#0280

24 - Cervical neoplasia

EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HPV INFECTED WOMEN: NORMALIZING HPV-DEPENDENT CERVICAL LESIONS (ASCUS/LSIL) AND HIGH-RISK HPV CLEARANCE

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Background/Objectives: In previous clinical studies a non-hormonal Coriolus versicolor-based vaginal gel (CVVG) has shown to significantly influence the re-epithelialization of the cervix and the rebalancing of the vaginal microbiota that favors the natural process of vaginal immunity. The objective was to evaluate the effect of the CVVG on the normalization of cervical HPV-dependent atypia (ASCUS and LSIL) and associated colposcopic alterations, and on the clearance of high-risk HPV (HR-HPV).

Methods: Multicenter, randomized, open-label, parallel-group, usual practice controlled clinical trial (Paloma Clinical Trial). Unvaccinated HPV+ women aged between 30 and 65 (mean age of 41 yo, evenly distributed among groups) with cytology of ASCUS or LSIL and concordant colposcopy image were included.Patients were randomized into 3 groups: A) CVVG 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months; B) CVVG 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months; C) Control group: no treatment (usual clinical practice). Percentage of patients with normalization of the lesions (normal cytology and concordant colposcopy image) as the primary endpoint and percentage of patients with HR-HPV clearance (secondary endpoint) were evaluated at 6 months.Pap smear evaluation and HPV identification (Clart® HPV4) were blind and centrally-conducted by an independent researcher at the IECM laboratory (Lugo, Spain). CVVG arms (A+B) were combined as treatment group and chi-square test was used.

Results: Atotal of 84 patients (total population) were evaluated (53 vs 31 in treatment and control groups, respectively) of which 66 were HR-HPV (HR-HPV subpopulation) (41 vs 25 in treatment and control groups, respectively). In the total population, 85% (43/53) of patients treated with CVVG had normal cytology with concordant colposcopy vs 65% (20/31) in control group (p=0.031). In the HR-HPV subpopulation, normal cytology and concordant colposcopy image was observed in 88% (36/41) of patients treated by CVVG vs 56% (14/25) of patients in control group (p=0.003).HR-HPV clearance was observed in 63% (25/40) vs 40% (10/25) of patients treated with CVVG and control group, respectively (p=0.076).

Conclusions: After the six-month treatment period,CVVG has shown statistically significant efficacy in normalizing HPV-dependent cervical lesions (cytology of ASCUS/LSIL and concordant colposcopy images), especially in HR-HPV subpopulation. A trend to increase HPV clearance has also been observed in HR-HPV subpopulation.

FC 05 Public Health / Education (I)

#0046

38 - Public health

Baseline human papillomavirus vaccination prevalence prior to extended Food and Drug Administration licensure for adults 27-45 years old in the United States

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Background/Objectives: The United States Food and Drug Administration recently approved the Human Papillomavirus (HPV) vaccination for people 27-45 years old. Increasing vaccination rates in this group is critical to reducing HPV-associated disease in a country with very low vaccine uptake. The objective of this study was to explore baseline HPV vaccination prevalence and factors associated with vaccination in the United States to identify future intervention targets in a country with relatively low vaccine uptake compared to other industrialized counties. Findings can be translated to other high income countries that may also have the infrastructure to deliver HPV vaccination to a large portion of the population, yet still have relatively low vaccine uptake including Japan, Denmark, and France.

Methods: We used a weighted, nationally representative sample from the 2017 United States National Health Interview Survey to assess prevalence of sup1 HPV vaccination for people 27-45 years old. We stratified by sex and assessed factors associated with HPV vaccination. Variables associated with vaccination at pinf0.1 in unadjusted logistic regression models were included in an adjusted model. Backward regression created a best-fit model in SAS 9.4.

Results: The sample (n=7,222) averaged 35.7 years old, majority were non-Hispanic White (57.6%), female (51.7%), married/living with partner (70.0%), and had health insurance (85.5%). One-tenth (9.7%) had ≥1 HPV vaccination (15.8% for females vs. 3.2% for males; $p<0.001$). In the best fit model, age was inversely associated with HPV vaccination (female: OR=0.84; 95%CI=0.81-0.86; male: OR=0.86; 95%CI=0.82-0.90). Non-Hispanic Black men had lower odds of vaccination (OR=0.27; 95%CI=0.11-0.67) and gay men had higher odds of vaccination (OR=3.09; 95%CI=1.48-6.41). Education was significant for females (Bachelor's degree OR=3.15; 95% CI=1.77-5.61). Marital status was significant for males (unmarried OR=2.87; 95% CI=1.43-5.78). Insurance coverage was not significant for either sex.

Conclusions: These data show there is significant room for improvement in HPV vaccination among 27-45 year olds in the United States. Future research both in the United States and internationally should focus on interventions to increase HPV vaccination particularly among men, underrepresented minorities, and those who do not regularly access healthcare.

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#0235

38 - Public health

The decision to extend HPV vaccination to adolescent boys in the UK

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Background/Objectives: The Joint Committee on Vaccination and Immunisation (JCVI) recently provided advice to the UK Government that led to a policy decision to extend the Human Papilloma Virus (HPV) immunisation programme to boys. We present the key scientific, economic and equality arguments considered. The JCVI is an independent expert committee that advises the UK Government on matters to do with immunisation. Based on JCVI's advice an HPV immunisation programme for girls was launched in 2008 with the aim of reducing the burden of cervical cancer. JCVI started considering the question of extending the HPV programme to boys in 2013 generating intense debate and lobbying from stakeholders, the media and parliament in the process. A key part of JCVI's decision making is cost-effectiveness. The NHS is a rationalised health system which aims to maximise health with the money at its disposal. Under current rules the threshold for cost-effectiveness is £20,000 per Quality Adjusted Life Year and in general a vaccine should not be accepted as cost-effective if there is an unacceptably high chance that its incremental cost-effectiveness ratio (ICER) exceeds £30,000. The objective was to provide final advice on whether to extend the HPV vaccination to adolescent boys.

Methods: The JCVI considered evidence on HPV epidemiology, natural history, vaccine immunogenicity and effectiveness, two independent impact and cost effectiveness models and consulted with stakeholders on the scientific evidence and equality. The cost-effectiveness of vaccinating boys was examined in an incremental analysis comparing the additional impact of vaccinating boys on that of a girls' only programme with a discount rate of 3.5% for costs and benefits.

Results: Under the standard rules, extending HPV immunisation to boys was shown to be highly unlikely to be cost-effective. This was because of the substantial herd protection to boys provided by high vaccine uptake in girls (>80%). The Committee noted, however, that because HPV associated cancers occur many years after infection, it could be argued that a 1.5% discount rate should be used rather than the standard 3.5%. The Committee also considered that comparing a combined girls' and boys' programme to a scenario of no programme could be more equitable. Both approaches showed a gender-neutral programme to be cost-effective and JCVI could advise extending HPV immunisation to adolescent boys.

Conclusions: JCVI has shown that making decisions on new or existing immunisation programmes is becoming more complex and that the wider issues of health economic methodology and other considerations, such as equality, need to be taken into account.

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#0500

38 - Public health

DETERMINANTS OF HPV-VACCINATION COVERAGE OVER TIME IN THE NETHERLANDS

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Background/Objectives: In the Netherlands, girls 12/13 years of age receive HPV-vaccination through the National Immunization Program (NIP) from 2010 onwards. Vaccination uptake during the catch-up campaign in 2009 for birth cohorts 1993-1996 was 56%. This increased to 61% for birth cohorts 2000 and 2001 in the regular program, but declined thereafter to 45.5% for birth cohorts 2003 and 2004. This study was aimed to gain insight into the relationship between social, economic, cultural and political factors and the HPV-vaccination coverage and whether the influence of these factors changed over time.

Methods: A database study was performed to study determinants of HPV-vaccination coverage on different aggregation levels: individual, postal code and municipality. The study population consisted of Dutch girls invited for HPV-vaccination through the NIP in the years 2012, 2014 and 2017 (birth cohorts 1999, 2001 and 2004). Two-level multivariate logistic regression analysis was conducted to analyze the influence of determinants on HPV-vaccination coverage, taking into account that individual-level variables were nested within the municipality-level variables.

Results: Results showed that ethnicity, socioeconomic status, urbanization level and voting proportions in national elections were related to HPV-vaccination coverage. In particular girls with one or two parent(s) born in Morocco, Turkey or Netherlands Antilles/Aruba, a lower socioeconomic status, a higher urbanization level in 2012 and 2014 and higher voting proportions in municipalities for the Protestant-Christian political parties (CU and SGP) and right-winged conservative parties (PVV and FvD) were associated with a lower HPV-vaccination coverage. In several variables we found some small changes between the vaccination years, however, we did not find clear factors which could possibly explain the decrease in the HPV-vaccination coverage.

Conclusions: This study gives insight into the relationship between social, economic, cultural and political factors and the HPV-vaccination coverage for public health relevance. Tailored information and/or consultation can be prepared for identified target groups that are associated with a lower HPV-vaccination coverage. This might help to increase the HPV-vaccination coverage in the Netherlands.

#0065

35 - Advocacy, acceptability and psychology

HPV VACCINE COVERAGE IN CATCH-UP COHORTS IN THE ANCONA AREA, ITALY

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Background/Objectives: Italian Regions introduced HPV vaccination programmes starting in 2007, with different target ages and payment regimes for catch-up groups. Previous research has shown that higher vaccine availability, lower financial barriers, and interventions targeting both providers and patients are positively associated with HPV vaccine uptake (1). We aimed at retrospectively assessing the trend of HPV vaccine coverage in catch-up cohorts in the area of Ancona, Marche Region (Italy), to verify the impact of the promotion strategies adopted.

Methods: We checked HPV vaccination coverage in the Ancona area of the Marche Region in Italy, for girls born from 1986 to 1993, targeted by the catch-up vaccination programme.

Results: Totale female population in the included cohorts amounted to 18,859, while overall HPV vaccine coverage was 12.3% (one dose) and 11.6% (three doses). In March 2019, HPV vaccine coverage by birth cohort was, from the 1986 to the 1993 cohort: 0.3%, 0.4%, 0.6%, 0.9%, 2.5%, 24.9%, 28.3%, and 43.0%. Cohorts 1991, 1992, and especially 1993 show a markedly higher coverage, and three moments of improved uptake are observable in years 2009, 2011 and 2012. Coverage rates then reached a plateau and have remained stable since.

Conclusions: The Italian Government actively promoted HPV vaccination, starting in February 2008 with a speech by the Minister of Health (2). In the Marche Region, where the vaccine was actively offered for free only to the primary target group (the 1997 cohort), a July 2009 regional resolution extended the free offer to older girls (3). Specifically, co-payment was eliminated for those born in 1991 and later, which explains the rising coverage, from the end of 2009, in cohorts 1991 to 1993. The two sharper coverage increases at the start of 2011 and 2012 correspond to two subsequent active invitations of the girls by letter. These findings confirm the positive association between vaccine uptake and its availability and affordability, suggesting, furthermore, that the younger girls were more prone to getting vaccinated, possibly because of a higher perceived benefit.

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#0275

35 - Advocacy, acceptability and psychology

ETHNIC DIFFERENCES IN INTENTION OF DAUGHTERS VERSUS PARENTS TO VACCINATE AGAINST HPV IN AMSTERDAM, THE NETHERLANDS

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Background/Objectives: In the Netherlands, HPV vaccination is currently only offered to girls in the year they turn 13 years of age. Compared to other childhood vaccinations HPV vaccination coverage is low in the Netherlands (~45%) and even lower among ethnic minorities. In 2014, the Public Health Service (PHS) of Amsterdam studied the acceptability of HPV vaccination among parents of Dutch and non-Dutch origin and found similar determinants influencing intention and uptake between both groups [1]. However, these determinants explained HPV vaccination uptake to a lesser extend in non-Dutch parents compared to Dutch parents. As daughters might play a key role in this decision-making process, in this study we explore how the 12/13 year old daughters are involved in making decisions on vaccinating against HPV.

Methods: In February 2014, parents/guardians and their 12/13 year old daughters living in Amsterdam were invited to complete a questionnaire about social-psychological determinants of the decision-making process regarding HPV vaccination. This questionnaire was sent approximately one month before the scheduled date of the first vaccination. Vaccination status of the daughter was later retrieved from the national vaccination database. Analyses were stratified by origin of parents (Dutch versus non-Dutch).

Results: In total, 439 parent-daughter couples with data of both parents and their daughters were analysed for this study (273 Dutch couples and 166 non-Dutch). HPV vaccination uptake was 90.1% (246/273) and 84.3% (140/166) in the Dutch and non-Dutch group, respectively. In the Dutch group, parental intention (OR 5.07, 95% CI 2.28-11.31) was more strongly associated with HPV vaccination uptake than that of their daughter (OR 2.03, 95% CI 0.89-4.60). In contrast, in the non-Dutch group, daughters' intention (OR 3.52, 95% CI 1.80-6.88) was more strongly associated with HPV vaccination uptake than that of their parents (OR 1.09, 95% CI 0.62-1.93). Socio-psychological factors associated with intention to vaccinate for parents and/or daughters were, among others, attitude, beliefs (e.g. long-term consequences), social norms (both subjective and descriptive), and more distal factors, such as the amount of information processed and evaluated, confidence in authorities, and strength of habits.

Conclusions: In the non-Dutch group, HPV vaccination is driven mostly by daughters' intention, whereas it is mostly driven by parental intention in the Dutch group. New health-promotion efforts regarding HPV vaccination might need to be tailored to take these ethnic differences into account in an effort to increase vaccination uptake.

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#0552

35 - Advocacy, acceptability and psychology

THE AFFORDABLE CARE ACT AND RATE OF HUMAN PAPILLOMAVIRUS (HPV) VACCINE UPTAKE IN THE UNITED STATES

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Background/Objectives: The United States has experienced modest increase in HPV vaccination uptake in the last decade, but remain short of the goal of vaccinating 80% of eligible adolescents by the year 2020. One known factor (barrier) associated with vaccine uptake is cost. The Affordable Care Act (ACA) came into full effect in 2014 in the United States, with an overarching aim to increase access to preventive healthcare services, including recommended vaccines, such as the HPV vaccine. This study aimed at evaluating the association between the ACA and known HPV vaccination-enabling factors in the United States.

Methods: The National Health Interview Survey was queried for individuals 18-26 years from 2011 to 2017. Changes in vaccination-enabling factors (regular physician visitation [defined as physician's visit within 12 months], and changes in health insurance status), and HPV vaccination status pre- (2011-2013) to post-ACA (2014-2017) were assessed using logistic regression models adjusted for poverty, education, marital status, comorbidities, sex, and geography. We defined HPV vaccine initiation as receiving a single vaccine dose, and completion as receiving ≥2 doses.

Results: A total of 13,494 and 15,722 eligible individuals were identified pre- and post-ACA. There was a 43% increase in HPV vaccine initiation post-ACA (3.9% to 5.5%; OR 1.45, 95% CI 1.24, 1.70; p<.001), with increases primarily among non-Hispanic whites (OR 1.55, 95% CI 1.24, 1.94; p<.001) and blacks (OR 1.59, 95% CI 1.12, 2.29; p=.009). Additionally, both rate and odds of HPV vaccine completion (receiving ≥2 HPV vaccine doses) increased significantly post-ACA (12.5% to 17.8%; OR 1.62, 95% CI 1.47, 1.79; p<.001); and this increase was mostly associated with Hispanics (7.6% to 14.7%), compared with non-Hispanic whites (ORinteraction = 1.36, 95% CI 1.05, 1.77; p=.020). Post-ACA, there was significant decrease in uninsured rates, and increases in vaccination completion odds among individuals privately insured (OR 1.36, 95% CI 1.22, 1.52; p<.001), and those under Medicaid (OR 1.81, 95% CI 1.35, 2.43; p<.001). There was also a corresponding increase in the rate and odds of regular physician visitation post-ACA (53.1% to 57.1%, OR 1.17, 95% CI 1.09, 1.25; p<.001).

Conclusions: The ACA is associated with increased HPV vaccination uptake, with significantly greater increases in HPV vaccination completion among ethnic minorities. These gains might be driven by an increase in vaccination-enabling factors such as decreased uninsured rates and increased physician visits.

#0193

38 - Public health

DESIGN AND CONTENT VALIDATION OF A SURVEY QUESTIONNAIRE ASSESSING THE DETERMINANTS OF HPV VACCINE HESITANCY IN FRANCE: A DELPHI STUDY.

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Background/Objectives: The determinants of HPV vaccine hesitancy (VH) in France, where HPV vaccine uptake is low, need to be thoroughly evaluated. There is currently no specific tool to assess those in France. This study aimed to develop and undertake a preliminary validation of a French Survey Questionnaire for the Determinants of HPV Vaccine Hesitancy (FSQD-HPVH), using the WHO Strategic Advisory Group of Experts (SAGE) Vaccine Hesitancy Model of Determinants as a framework (1).

Methods: We undertook an electronic-based Delphi consultation among a panel of Francophone experts, in two rounds. Round 1 consisted of the assessment of a structured questionnaire comprising of three parts ((i) Contextual influences, (ii) Individual and group influences, and (iii) Vaccine/vaccination-specific issues) and many subparts, in line with the SAGE Model. Items included in this questionnaire were based on literature review. Definitions of the factors included in the SAGE Model were provided in the questionnaire. The panel of experts was asked to score each item using a 3-point Likert scale, in which 1 meant "Essential", 2 "Useful but not essential", and 3 "Not necessary". The panel was also invited to comment on the clarity/comprehension of the items and suggest reformulations and additional items that may have been missing. Lawshe's Content Validity Ratio (CVR) (2) was computed to assess the level of consensus for each statement. Only items upon which agreement was not reached in Round 1 (CVR<0.6) and newly proposed items (as per the panel's suggestions) were submitted for evaluation in Round 2, using the same procedure.

Results: Fifteen experts (6 health care professionals and 9 academic teachers/researchers, see Table 1 for details) completed Round 1. All panel members were France-based except two (from Canada and the UK). Of 83 items evaluated in Round 1, 35(42%) had a CVR greater than or equal to 0.6 and were thus retained for the final survey questionnaire. In Round 2, a total of 66 items were submitted to the same expert panel, including 48 old items that did not reach consensus at Round 1 - recirculated either as initially worded (n=23) or after rewording (n=25) - and 18 new ones. All the fifteen experts completed Round 2, reaching consensus for 22(33%) items (8 as initially worded, 8 reformulated following Round 1, and 6 newly proposed at Round 2). The final version of the questionnaire includes 57 items.

Conclusions: In conclusion, 57 items of FSQD-HPVH with good content validity were developed in this study. Unlike the existing tools, the FSQD-HPVH is the first to comprehensively consider the factors that may influence HPV VH. This research paves the way for a larger research project, the next stage consisting of the FSQD-HPVH pilot-testing and large-scale administration, which will allow further evaluation of its validity. Adequate assessment of the determinants of HPV VH is the first step towards an evidence-based approach to curbing low HPV vaccination rates in France.

References: (1) Larson HJ et al. Measuring vaccine hesitancy: The development of a survey tool. Vaccine 2015. (2) Lawshe CH. A quantitative approach to content validity. Pers Psychol 1975.

#0237

5 - HPV prophylactic vaccines

KNOWLEDGE OF HUMAN PAPILLOMA VIRUS INFECTION AND ATTITUDES TOWARDS ITS VACCINE

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Background/Objectives: Genital HPV is common and affects both men and women. Infection with the high-risk oncogenic HPV types 16 and 18 is a known cause of cervical cancer. The objective of this study is to determine the level of awareness of HPV infection, and to assess attitudes towards receiving the vaccine amongst men and women in Bahrain.This study can aid communication between health policy makers to include HPV vaccine in the national immunization schedule.

Methods: This isa cross-sectional study of 408 males and females attending the primary health care centers in the Kingdom of Bahrain. A cluster multistage sampling method was used to select the included primary health care centers. An interview-based questionnaire was used to assess HPV knowledge and attitude towards HPV vaccine. The demographic and baseline variables were summarized using descriptive statistics; Chi square test was used to investigate the association between the categorical variables of socio-demographics, knowledge and attitudes. Statistical significance was set at p-value of <0.05.

Results: A response rate of 91.4% was achieved, with majority being female responders (65.7%).Only 13.5% of the participants had heard of HPV. Majority of the participants (76%) were willing to take the vaccine if recommended, with 84.4% believing that both genders should be vaccinated. However, 48.5% were concerned about possible side effects of the vaccine. More than 90% of the participants agreed on the need for educating the community about the HPV infection. More than half of the study sample (60%, 244) thought that the vaccine is safe but 83.6% (341) wanted to be reassured that the vaccine would protect against HPV.

Conclusions: Overall, the findings showed poor awareness of HPV, which is not surprising, considering the lack of public education regarding the virus and absence of HPV vaccination in the national immunization schedule.Despite the limited knowledge about HPV infection among the study's participants, there is a favorable attitude towards the HPV vaccine. Predominance for accepting the vaccine was also accompanied with worries regarding possible side effects. Our findings demonstrate the need to provide education to the Bahraini community about HPV infection and the role of HVP vaccine. We have highlighted some significant gaps in HPV knowledge that can be the target of future information campaigns. Poor awareness in men may pose a particular challenge as and when HPV vaccination for males becomes available.

FC 06 - Low resource settings

#0220

9 - HPV screening

PREVALENCE AND DETERMINANTS OF HUMAN PAPILLOMAVIRUS INFECTION AND CERVICAL INTRAEPITHELIAL NEOPLASIA AMONG FEMALE SEX WORKERS IN MUMBAI,INDIA

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Background/Objectives: Human papillomavirus infection (HPV) being essentially a sexually transmitted infection (STI), high risk behaviour women with multiple sexual contacts like Female Sex workers (FSW) are at higher risk of co-infection with HPV and of developing cervical precancer and cancer. This study aimed to determine the prevalence and determinants of HPV infection and cervical intraepithelial neoplasia (CIN) among female sex workers (FSWs) in Mumbai,India.

Methods: Total 448 FSWs between the ages of 18- 50 yrs were recruited from designated red light districts in Mumbai, India. Information on socio demographic and sexual behavioral characteristics were obtained via structured pretested questionnaire. All FSWs were screened for HPV DNA by Hybrid Capture II and VIA (visual inspection with acetic acid) followed by colposcopy and/or cervical biopsy. Association between HPV DNA positivity and sociodemographic, sexual behavioral factors was estimated with age-adjusted odds ratios and 95% confidence intervals using logistic regression analysis.

Results: The overall high risk HPV prevalence was 35.5% and 12.5 % of them were tested positive on VIA. The prevalence of CIN II and above lesions was 1.3%. HPV prevalence was higher among FSWs in age group less than 25 yrs ($p<0.001$), had no formal education ($p=0.002$), not exposed to the Sexually Transmitted Diseases/Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (STD/HIV/AIDS) education program (p-0.043), currently single ($p<0.001$), with first sexual experience at less than 18 years($p=0.028$), had never or rarely uses barrier contraception ($p=0.026$), with more than 2 pregnancies ($p<0.001$) and those with STI symptoms in the recent 12 months ($p=0.005$).

Conclusions: FSWs have a high prevalence of HPV infection and are at increased risk of cervical cancer. Cervical cancer awareness and screening is not part of any health care interventions currently targeted towards them. With the inherent social, cultural barriers faced by these high-risk population to access cervical cancer screening programs,and because of their common epidemiological determinants, the scope of the current national program for STD/HIV AIDS prevention and control should be expanded to cover cervix cancer prevention and screening which will be highly cost-effective to decrease the burden of cervical cancer among FSW.

#0306

8 - HPV testing

High-risk Human Papillomavirus Messenger RNA Testing in Wet- and Dry- self-collected specimens for cervical lesion detection among high-risk women in Mombasa, Kenya

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Background/Objectives: High-risk HPV (hr-HPV) mRNA testing may improve cervical cancer screening. HR-HPV mRNA testing using self-collected specimens stored in liquid media (stored wet) shows comparable performance to physician-collected specimens. HR-HPV mRNA with self-collected specimens stored dry could enhance the feasibility of specimen collection and storage, however, the performance of dry-stored specimens for detection of high-grade cervical lesions or higher (≥HSIL) is unknown. We compared the performance of hr-HPV mRNA testing with dry-and wet-stored self-collected specimens for detecting ≥HSIL.

Methods: A total of 400 female sex workers in Kenya participated (2013-2018), of which 50% were HIV-positive based on enrollment procedures. Participants provided two self-collected specimens: one stored dry (sc-DRY) using a Viba brush (Rovers), and one stored wet (sc-WET) with Aptima media (Hologic) using an Evalyn brush (Rovers). Two physician-collected specimens were collected for HPV mRNA testing (APTIMA) and for conventional cytology. We estimated test characteristics for each hr-HPV screening method using conventional cytology as the gold standard. Differences in sensitivity and specificity screening tests were assessed using Wald-type confidence intervals. We also examined participant preference.

Results: For all three individual HPV-mRNA screening tests, the prevalence of hr-HPV mRNA was higher among HIV-positive women compared to HIV-negative (sc-WET: Prevalence difference (PD) 0.15, 95%CI: 0.06-0.24; sc-DRY: PD 0.14, 95% CI: 0.04-0.23; physician: PD 0.19, 95% CI: 0.10-0.28). HR-HPV mRNA positivity was higher in sc-WET (36.8%) than sc-DRY samples (31.8%). Prevalence of ≥HSIL was 6.9% (n = 27). Sensitivity of hr-HPV mRNA testing for detecting ≥HSIL was similar in sc-WET (85.2%, 95% CI: 66.3-95.8) and sc-DRY specimens (77.8, 95% CI: 57.5-91.4) (Difference: -0.07, Wald 95% CI: -0.21 to 0.07). Overall, the specificity of hr-HPV mRNA for ≥HSIL detection was similar when comparing sc-WET to physician-collection (Difference: -0.03, 95% CI: -0.08 to 0.01). However, specificity was lower for sc-WET [66% (61-71)] than sc-DRY [71% (66-76)] (Difference: -0.05, 95%CI: -0.10 to -0.00). Women preferred sc-DRY specimen collection (46.1%) compared to sc-WET (31.1%). However, more women preferred physician-collection (63.9%) compared to self-collection (36.1%).

Conclusions: HR-HPV mRNA prevalence was lower in dry- than wet-stored self-collected specimens. Sc-DRY specimens appeared to perform similarly as sc-WET for the detection of ≥HSIL. However, women's preference for either type of self-collection method was lower than physician-collection.

#0067

37 - Low resource settings

Attendance to follow-up cervical cancer screening among rapid careHPV-positive Tanzanian Women: a randomised trial and post-trial qualitative study

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Background/Objectives: Rapid HPV DNA testing is an emerging cervical cancer screening strategy in resource-limited countries but it requires follow-up of women who test HPV-positive. We conducted a parallel-group randomised trial to determine if one-way text messages (SMS) improved attendance to a 14-months follow-up cervical cancer screening among HPV-positive women. Post-trial, we assessed how attendance could be increased via phone calls and home visits. Further, we interviewed a sub-group of women post-trial to understand causes of non-attendance.

Methods: The trial was conducted at three hospitals in Tanzania. Eligible participants were 25-60 years and had tested positive to a rapid careHPV-test during a patient-initiated screening. Participants were randomly assigned 1:1 into the intervention or control group. The intervention group received one-way educative and reminder SMS, and the control group received no SMS. Participants were not blinded but outcome assessors were. The analysis was intention-to-treat [1]. The qualitative post-trial study was conducted at a hospital or in the homes of the participants. Semi-structured individual interviews were conducted with women appointed for a health provider-initiated follow-up screening. Further, cervical cancer screening nurses were interviewed. Data was analysed through a content analysis [2].

Results: Between August 2015 and July 2017, 4080 women were screened for cervical cancer of which 705 were included in the trial; 358 were allocated to the intervention group and 347 to the control group. Sixteen women were excluded prior to analysis due to developing cervical cancer or dying. In the intervention group, 84 women (24%) attended their screening, and in the control group, 80 women (24%) attended (RR: 1.02; 95% CI: 0.79-1.33). Post-trial, an additional 24% attended their screening at the clinic when they had been called and/or had a nurse home visit, and a further 30% had their screening via a home visit and a self-sample test [3]. 15 interviews were conducted with screening clients and two interviews with screening nurses. Perceived benefits for attending a patient-initiated screening were treatment of gynecological symptoms and prevention of disease. The key benefit of a health provider-initiated follow-up screening was prevention, which could be postponed when competing needs were present. Perceived challenges included fear of the disease and the examination, transportation costs, and waiting time [2].

Conclusions: Attendance to a health provider-initiated follow-up cervical cancer screening among HPV-positive women was strikingly low. Implementation of rapid HPV-testing at clinic level entails a challenge of ensuring a proper follow-up of women.

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#0311

37 - Low resource settings

Towards cervical cancer control: Opportunities and challenges in low- and middle-income countries (LMICs)

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Background/Objectives: Effective screening for precancerous lesions of the cervix is the only preventive intervention for women that have not been vaccinated or are outside the target age range for vaccination. International agencies are establishing a focused agenda towards the global control of cervical cancer. Although technological and scientific advances have been made to push screening towards a low cost, effective, and sustainable approach, many unanswered questions remain in regards to impactful interventions in low- and middle-income countries (LMICs). Bringing screening to scale at a national level will require self- or provider-collected vaginal specimens, human papillomavirus (HPV) testing, linking screen-positive women with a high performing triage test (which remain unavailable in many LMICs), and accessible treatment. Women living with HIV may warrant different screening approaches.

Methods: Drawing from PATH's experience scaling up HPV testing in three Central American countries, we outline opportunities and challenges for improving cervical cancer screening in LMICs.

Results: Specifically, self-sampling was key in reaching 230,000 women across the three countries, and a promising new approach, thermal ablation, consistently increased treatment coverage in Guatemala and Honduras. The use of either Pap or visual inspection with acetic acid (VIA) demonstrated limited utility as triage tests. Specific efforts to ensure that women are effectively registered in the health system and followed-up are essential to improve adherence to screening recommendations.

Conclusions: The main challenge of a triage test may be mitigated by the forthcoming automated visual evaluation (AVE) for HIV-uninfected HPV-positive women. Ongoing research will soon provide critical information on the global applicability of AVE. In addition to innovative biomedical interventions, it is paramount to address local social, economic, and behavioral factors that influence implementation and uptake of screening and treatment in LMICs. As HPV scientists, we can play a role in acknowledging the limitations of current screening approaches and championing a bold multidisciplinary operational research agenda to identify and design the next steps to achieve cervical cancer control.

#0450

37 - Low resource settings

Lesson Learned for Developing and Transferring Cervical Cancer Screening Technology to Low Middle Income Countries (LMIC)

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Background/Objectives: AmpFire HPV screening assay designed and developed with the developing world in mind by a team in Silicon Valley after 10 years of dedicated research. The assay demonstrated that is very simple to run and very inexpensive, and good for dry brush transport to be used with self-collected vaginal samples. Self-collection can become an important addition to population based cervical cancer screening programs as the primary screen in LMIC. Objective of this presentation is to share the evolution of designing and developing the AmpFire HPV screening technology suitable for LMIC and lesson learned for how to transfer the technology to LMIC.

Methods: ASSAY METHODS: The AmpFire Multiplex HR HPV Screening assay detects 15 HR HPV and simultaneously genotypes HPV 16 and 18 in one reaction plus an Internal Control (IC) with isothermal real time fluorescent detection. An example of detection dry brush HPV sample, after adding 1ml chemical buffer to the dry brush sample tube with vortexing and waiting for 20 minutes at room temperature, it is then ready to be added (2ul) to the reaction tube for detection. The HPV results are automatically reported by Atila detection system within an hour.

Results: RESULTS AND DISCUSSIONS: In resource-limited environments, the practicality of collecting and processing a particular specimen type is one of the most important factors in the successful adoption of a particular test. Self-collection and dry brush samples overcome many of the barriers comparing to use of alcohol-based liquids for cervical cancer screening because it is hazardous and not flexible for transportation. AmpFire HPV assay was used in Inner Mongolia to screen 1400 women in two days with an overall positive rate of proximately 18% on self-collection dry swabs. The workflow will be discussed and experience and lesson learned to transfer AmpFire HPV assay to Rwanda, Zimbabewe, Ghana, Gambia, Colombia, Senegal, India, Ethiopia, Indonesia will be shared.

Conclusions: CONCLUSION: AmpFire HPV assay is suitable for being used in LMIC for large population screen. It is affordable at a fraction of the cost of common assays. To able to use dry swab sampling is much easy to collect, but still meet the sensitivity and specificity. The test is simple to perform and interpret with minimal training. Sample to result is about an hour that is fast enough to enable treatment of the patient during the visit. AmpFire have good tolerant with great reproducibility. The test is portable and function under a wide range of conditions

#0357

10 - Self-sampling

HPV Self-testing RCT in Indigenous population: interim results.

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Background/Objectives: In Aotearoa New Zealand, the National Cervical Screening Program (NCSP) using the standard speculum examination for cytology, is failing indigenous Māori women, with 33% unscreened compared to 24% of NZ European/other women unscreened. (1) Māori women are more than twice as likely to die of cervical cancer than NZE women and these cancers are preventable. (2, 3) Oncogenic HPV testing is more effective in detecting pre-cancer changes on the cervix and preventing cervical cancer, than conventional cytology. (4) Self-collected specimens (self-testing) can be used for HPV testing, providing screening with comparable sensitivity and specificity to clinician-collected specimens. (5) This community based RCT offered HPV self-test to under-screened Māori women in partnership with Māori communities and primary care practices. The overall aim was to increase cervical screening coverage and in this presentation we will share the methodology and interim results showing uptake among the intervention group of under-screened Māori women.

Methods: Inclusion criteria were Māori women aged 25-69 years, who had not had a cervical smear screen in 4 years or more. Six primary care clinics in a rural area of Northland were randomised to intervention (offer of self-swab) and control (usual offer of cervical smear). A list was generated by the clinics of women fulfilling the criteria. Recruitment started on 5th March 2018 and ended on 31st August 2019. HPV genotyping was carried out using the Abbott Real-time High Risk HPV assay distinguishing HPV-16 and HPV-18 from other high-risk types and from negative samples.

Results: To date in the intervention group there were 530 under-screened Māori women. Of these 30 had had a hysterectomy or died and were excluded. Of the 500 eligible women, 263 (52.6%) accepted the swab, 24 (4.8%) chose a cervical smear. Thirty women (6%) declined the swab, 28 had incorrect contact details and were not contactable, 81(16.2%) had moved leaving 76 (15.2%) women who were contacted multiple times and who did not decline outright but did not have a swab despite the efforts by clinic staff to offer clinic appointments or home visits. Of the total 263 swabs, 233 (88.6%) were taken by the patient, and 30 (11.4%) were taken by the nurse/doctor or other. Of those that had a screen (n =283) 35 had results positive for HPV 16, 18 or "other' and were referred to colposcopy

Conclusions: We conclude that self-screening for HPV has the potential to half the number of under-screened Māori women. This test is acceptable and liked by women who choose not to have a cervical smear and should be incorporated into the new NCSP in Aotearoa as soon as possible to decrease the morbidity and mortality caused by cervical cancer and decrease inequities in health care.

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FC 07 - Epidemiology and natural history (III)

#0015

2 - Epidemiology and natural history

Human papillomavirus genotype and prognosis of invasive cervical cancer: A nationwide cohort study

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Background/Objectives: The role of human papillomavirus (HPV) in development from oncogenic infection to invasive cervical cancer (ICC) has been well established. Our earlier study showed high-risk HPV in tumor was associated with better prognosis of ICC. However, the association of HPV genotypes and prognosis of ICC is controversial. Therefore, we aim to provide evidence on specific HPV genotypes and prognosis of ICC using Swedish register data.

Methods: We identified all ICC diagnosed in Sweden during the years 2002-2011 (4254 confirmed cases after clinical and histo-pathological review), requested all archival formalin-fixed, paraffin-embedded blocks and subjected them to comprehensive HPV genotyping. Twenty out of twenty-five archives agreed to the study, contributing a total of 2845 confirmed cases with valid HPV results. Cases were followed up from date of cancer diagnosis to 31 December, 2015, migration from Sweden, or death; whichever occurred first. Five-year relative survival ratios (RSRs) were calculated and excess hazard ratios (EHRs) with 95% confidence intervals (CIs) were estimated using Poisson regression.

Results: HPV was detected in 2365 tumors (83.1% of all cases). The five-year RSR by tumor HPV status was 0.54 (HPV negative), 0.76 (HPV16 positive), 0.73 (HPV18 positive), 0.72 (other high-risk HPV positive) and 0.56 (low-risk HPV positive) compared to the age-matched general female population. Compared to cases with HPV-negative tumor, a significantly lower excess mortality was seen if the tumor was positive for HPV16 (EHR:0.54, 95% CI 0.44-0.65), other high-risk HPV (EHR:0.47, 95% CI 0.37-0.60), and low-risk HPV (EHR:0.48, 95% CI 0.32-0.74), after adjustment for age, time since cancer diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, educational level and histology. However, the mortality among women with HPV18 positive tumors were not statistically significantly different from cases with HPV-negative tumors. In women with a single HPV infection of either HPV16 or HPV18, those with HPV18-positive tumors had 56% (EHR:1.56, 95% CI: 1.13-1.97) higher excess mortality compared to women with HPV16-positive tumors.

Conclusions: HPV genotype in cervical cancer tumor is associated with prognosis of ICC. Single HPV18 positivity indicated a poorer prognosis than single HPV16 positivity. This could add information of value beyond the established clinical prognostic factors for women diagnosed with ICC.

#0102

24 - Cervical neoplasia

FACTORS PREDICTING THE SPONTANEOUS REGRESSION OF CERVICAL HIGH GRADE SQUAMOUS INTRA EPITHELIAL LESIONS (HSIL/CIN2).

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Background/Objectives: To determine clinical, pathological and virological factors predicting the spontaneous regression of HSIL/CIN2.

Methods: Retrospective study of 73 patients with HSIL/CIN2 diagnosed on biopsy between 2012 and 2016 and followed-up without treatment. All patients had adequate visualization of the lesion and the squamo-columnar junction. Each biopsy has been reviewed by 2 pathologists independently. The expressions of p16 and Ki67 were evaluated on each biopsy. HPV genotype was detected in cervical smear samples at inclusion. Follow-up visits included colposcopy, cytology +/- biopsy every 6 months. The primary endpoint was the regression or the disappearance (response) of HSIL/CIN2 described by the regression or the disappearance of initial colposcopic findings (minor change or less), of cytological (LSIL or less), and histological results (LSIL/CIN1 or less).

Results: The baseline characteristics of the patients were as follows: median age 30 years (range, 21-40); 52 (38%) were current smokers; 68 (93%) were diagnosed with HR-HPV and 40 (55%) with HPV-16; 47 (64%) had ASCUS or LSIL and 26 (36%) had ASC-H or HSIL. The lesion was diagnosed as minor change (62%) or major change (38%) by colposcopy; the surface of the lesion was 2 quadrants or less (71%) or 3 quadrants or more (29%). P16 and Ki67 were overexpressed in 97% and 78% of cases, respectively. The review of biopsies sampled in (29%) or outside (71%) our center confirmed HSIL/CIN2 (90%), underdiagnosed LSIL/CIN1 (6%) or overdiagnosed HSIL/CIN3 (4%). The median duration of follow-up was 20 months (range, 6-55). The lesion spontaneously regressed or disappeared in 41 (58%) patients. The response rate in women with ASCUS/LSIL cytology was significantly higher than in women with ASC-H/HSIL cytology at baseline (69% vs 38%, p=0,012). The response rate in women with HSIL/CIN2 and HPV not 16 was significantly higher than in women with HSIL/CIN2 and HPV-16 (72% vs 46%, p=0,027). The response rate in women with HSIL/CIN2 diagnosed on minor change by colposcopy was significantly higher than in women with major change (67% vs 42%, p=0,033).

Conclusions: At baseline, cytological results (LSIL or less), genotyping (detection of HR-HPV not 16), and colposcopic findings (minor change or less) were factors predicting spontaneous regression of HSIL/CIN2. Other factors, like the age or the surface of the lesion, did not influence the outcome.

#0505

2 - Epidemiology and natural history

DIRECTIONALITY OF HPV INFECTION TRANSMISSION WITHIN HETEROSEXUAL COUPLES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background/Objectives: The EUROGIN 2014 Roadmap suggested greater female-to-male (F-M) relative to male-to-female (M-F) HPV transmission rates based on five couple-based longitudinal studies. We verified this proposed differential transmission rate hypothesis in couple-based studies by conducting a systematic review and meta-analysis.

Methods: We systematically searched MEDLINE, EMBASE, Scopus, and Cochrane Library databases from inception until June 10th, 2019. Studies were eligible if they included heterosexual couples aged 18 years and over, genital samples collected from couples, and reported transmission rates of alpha-HPV types. Two reviewers independently assessed the eligibility of the selected articles and abstracted the data. We summarized each study for transmission rates, number of transmission episodes, and person-time of follow-up. We examined the directionality of absolute transmission by calculating pooled estimates of F-M and M-F transmission rates, as well as rate differences per 100 person-months along with corresponding 95% confidence intervals (CI) using a random-effects model based on the number of transmission episodes and person-time. We quantified heterogeneity among studies using the I2 statistics. We also identified and counted occurrences of directionality preponderance (F-M or M-F) for each HPV type individually in studies that reported incidence/transmission rates by sex and HPV type. For these analyses, we considered the incidence rates in males and females to infer directionality under the assumption that HPV transmission occurred between study partners.

Results: Of 834 identified records, the full-text of 23 potentially relevant publications - based on the title/abstract screening - was obtained, of which 7 studies published between 2008 and 2019 were considered eligible. These included the 5 articles from the EUROGIN 2014 Roadmap and 2 more recent articles. Data from 752 couples were used in the analysis. The pooled estimate for F-M transmission rates was 3.01 (95% CI: 1.19-7.64), whereas that for M-F was 1.60 (95% CI: 0.86-2.98). The corresponding I2 statistics were 97% and 89%. The overall rate difference between F-M and M-F transmission rates was 0.61 (95% CI: -0.27-1.49) with an I2 value of 75%. Only three studies provided incidence/transmission rates by sex and HPV type. Two favoured a preponderance of F-M transmission (F-M>M-F for 16 genotypes vs M-F>F-M for 11 genotypes; F-M>M-F for 29 genotypes vs M-F>F-M for 6 genotypes), and one study favored a M-F transmission (F-M>M-F for 6 genotypes vs M-F>F-M for 14 genotypes).

Conclusions: Our findings provide moderate evidence for a differential transmission rate with higher F-M compared to M-F transmission. These finds must be interpreted with caution, however, because of the presence of substantial statistical heterogeneity.

#0013

9 - HPV screening

Human Papillomavirus DNA in surgical smoke during cervical loop electrosurgical excision procedures and its impact on the surgeon

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Background/Objectives: The purpose of this study was to explore whether human papillomavirus (HPV) DNA is present in surgical smoke generated by loop electrosurgical excision procedures (LEEPs). Furthermore, we investigated the impact of this HPV DNA on surgeons.

Methods: A total of 134 outpatients with persistent HPV infections treated with LEEP for cervical intraepithelial neoplasia between 2015 and 2016, along with the corresponding LEEP operators, were included. The flow fluorescence hybridization technique was used to detect HPV DNA in exfoliated cervical cells from the patients, in surgical smoke and in nasal epithelial cells from the surgeons before and after LEEP.

Results: The positive rates of HPV DNA in the above mentioned 3 sample types were 94.8%, 29.9% and 1.5%, respectively. The distribution of HPV subtypes in surgical smoke was identical to that in the cervical specimens. The positive rate of HPV DNA in surgical smoke was significantly increased for greater distances of the suction device from the surgical site. The nasal epithelial cells of two surgeons were positive for HPV DNA, and the genotypes were consistent with those in the corresponding surgical smoke. After a 3-6-month follow-up, the nasal swabs from these 2 doctors tested negative for HPV DNA.

Conclusions: This study demonstrated the presence of HPV DNA in surgical smoke produced by LEEP and the risk of airborne transmission of HPV DNA during the operation. Fortunately, the HPV DNA in the nasopharynx of the operators was not persistent.Key words: HPV; Loop electrosurgical excision procedure; Surgical smoke; Nasal swab

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#0415

2 - Epidemiology and natural history

HUMAN PAPILLOMAVIRUS INFECTIONS IN PREGNANT WOMEN IN NORWAY AND SWEDEN: A MULTI-CENTER POPULATION BASED PROSPECTIVE COHORT STUDY

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Background/Objectives: Human Papillomavirus (HPV) is one of the most common infections of the genital tract in women in their reproductive years. It is well established that High-Risk HPV (HR-HPV) infections cause dysplasia and cancer of the cervix as well as various other cancers. HPV prevalence, persistence and potential impact on pregnancy and neonatal outcome is however not clear. We therefore aimed to investigate HPV infections during pregnancy of unselected Norwegian and Swedish women, identifying prevalence and persistence, as well as determining HPV genotypes.

Methods: Unselected pregnant women in Norway and Sweden were enrolled to the large PreventADALL study (Preventing Atopic Dermatitis and ALLergies in Children)1 at the time of the routine ultrasound scan at gestational week 16-22. The HiPPiE sub-study (Human Papillomavirus in PrEgnancy) is a multi-center population based prospective cohort study. First void urine samples were collected at enrolment and at delivery and analyzed for HPV and genotyped on extracted DNA using Seegene Anyplex II HPV 28 Detection assay. This assay is a semi-quantitative real-time PCR test that detects and genotypes 12 HR-HPV, 7 probably or possibly HR-HPV, and 8 Low-Risk HPV types. For statistical analyses, high viral loads for a given HPV type were defined as positive samples with test results reported as (+++) or (++) in the Seegene Anyplex II 28 assay. In total 778 urine samples were collected at the time of enrolment and at delivery. In addition to this, comprehensive sociodemographic data was collected from the women using web-based questionnaires.

Results: Mean age of the total 778 enrolled women was 32.2 years and mean BMI was 24.4. The overall prevalence of HPV was 38.8% at mid-gestation (n=302)) and 26.9% at delivery n=209), and the corresponding prevalence of HR-HPV was 24.2% (n= 188) and 16.1% (n= 125) respectively. In HPV positive pregnancies, HPV 16 was the most prevalent genotype at both mid-gestation 6.0% (n=47) and at delivery 4.2% (n=33). Pregnancies infected with HPV 16, including multiple HPV infections, had higher persistence at delivery compared to other HR-HPVs, (61.7% vs 43.9%, p= 0.03). High HPV viral load at mid-gestation was associated with higher HPV persistence at delivery, most notably for HR-HPVs 16, 31 and 33.

Conclusions: A high prevalence of HPV of 39% at mid-gestation decreasing to 27% at delivery was observed in non-selected pregnant women, with the highest persistence rate observed among women with a high viral load of HR-HPV at mid-gestation. Our future studies will reveal whether HPV infections and persistence in pregnancy are associated with adverse maternal and neonatal outcomes.

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#0320

2 - Epidemiology and natural history

HPV-RELATED ANOGENITAL PRECANCER AND CANCER AMONG WOMEN WITH DIABETES IN DENMARK

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Background/Objectives: Some immunocompromising conditions are associated with an increased risk of human papillomavirus (HPV)-related disease. Although persons with diabetes have an increased risk of cancer and may be more susceptible to infections due to alterations of the immune system, little is known about HPV-related disease in diabetes patients. The aim of this nationwide, registry-based cohort study is to estimate the incidence of HPV-related anogenital precancer and cancer in women with type 1 and type 2 diabetes compared with women without diabetes.

Methods: We included the entire Danish female population born during 1916-2001 and identified those registered with diabetes in nationwide registries and clinical databases. The study population was linked to Danish pathology and cancer registries and followed for HPV-related anogenital (cervical, anal, vaginal, and vulvar) precancer and cancer during 1996-2016. We compared the incidence rates of HPV-related cervical and non-cervical (i.e. anal, vaginal, and vulvar combined) anogenital precancer and cancer among women with and without diabetes and estimated incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) using Poisson regression. Similarly, we estimated IRRs of cervical and non-cervical anogenital precancer and cancer among women with type 1 diabetes compared with women with type 2 diabetes. IRRs were adjusted for age, HPV vaccination, calendar time and educational level in all analyses.

Results: 2,457,393 women were included, and of these 171,917 women were classified as having diabetes during follow-up. The IRRs of cervical precancer and cancer were 0.74 (95% CI, 0.69-0.79) and 1.11 (95% CI, 0.98-1.26), respectively, in women with diabetes compared with women without diabetes. For non-cervical anogenital precancer and cancer, the IRRs were 1.45 (95% CI, 1.27-1.65) and 1.44 (95% CI, 1.27-1.64), respectively, in women with diabetes compared to women without diabetes. Comparing women with type 1 diabetes with women with type 2 diabetes, the IRRs were 0.84 (95% CI, 0.72-0.97) and 1.19 (95% CI, 0.79-1.77) for cervical precancer and cancer, respectively, and 0.87 (95% CI, 0.59-1.28) and 1.32 (95% CI, 0.78-2.22) for non-cervical anogenital precancer and cancer, respectively.

Conclusions: Women with diabetes had higher incidence of non-cervical anogenital precancer and cancer than women without diabetes. The incidence of cervical precancer in women with diabetes was lower than in women without diabetes, while the incidence of cervical cancer was higher. Women with type 1 diabetes tended to have lower incidence of cervical and non-cervical anogenital precancer than women with type 2 diabetes, but higher incidence of anogenital cancer.

#0111

2 - Epidemiology and natural history

THE RISK OF CERVICAL CANCER AFTER CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 3: A POPULATION-BASED COHORT STUDY WITH 80,442 WOMEN

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Background/Objectives: To estimate the risk of cervical cancer in women with a history of cervical intraepithelial neoplasia grade 3 (CIN3) compared to the general female population in the Netherlands. To review the compliance with the follow-up guidelines after CIN3 in women who developed cervical cancer.

Methods: A Dutch population-based retrospective cohort study including women with CIN3 between 1990-2010 obtained from the Dutch Pathology Registry (PALGA) and linked to the the general female population from the Netherlands Cancer Registry. Cases of recurrent CIN3 and cervical cancer, defined as occurrence after minimal 2 years post-treatment, were identified until 2016. Standardised incidence ratios (SIRs) were calculated for the risk of developing cervical cancer in women with CIN3 and recurrent CIN3. Excess relative risks were calculated with multivariable regression models.

Results: A total of 80,442 women were included, with a median age of 35.5 years (16.5-78.5) and a median follow-up of 15.8 years (2.1-27.0). The cohort comprised 1,278,297 person years. 1,554 women (1.9%) developed recurrent CIN3 and 397 women (0.5%) cervical cancer. Women with a history of CIN3 or recurrent CIN3 were associated with a twofold and ninefold increased risk of cervical cancer (SIR 2.29; 95%CI 2.07-2.52 and SIR 8.89; 95%CI 5.74-12.71, respectively) compared to the general female population. Women aged ≥50 years during diagnosis of CIN3 had a seven times higher risk of developing cervical cancer. The risk was the highest between 5-9 years of follow-up. The increased risk up to 20 years of follow-up seems to be mostly attributable to ageing. Of the women who developed cervical cancer after CIN3, 37.0% did not completed follow-up in the colposcopy clinic.

Conclusions: Women with a history of CIN3 have a long-lasting increased risk of developing cervical cancer, even when they complete the follow-up in the colposcopy clinic and return to the regular screening program, and is accentuated in women aged ≥50 years. Studies on follow-up strategies and vaccination after CIN3 to prevent this increased risk are warranted.

#0260

2 - Epidemiology and natural history

PRELIMINARY EVIDENCE OF THE BENEFICIAL IMPACT OF THE HPV VACCINE IN REDUCING HPV PREVALENCE IN MEN WHO HAVE SEX WITH MEN, SCOTLAND

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Background/Objectives: A targeted human papillomavirus (HPV) vaccination programme for men who have sex with men (MSM) aged up 45 years, was introduced in Scotland in July 2017. MSM are offered a three dose schedule of the quadrivalent vaccine through sexual health clinics and first year uptake of at least one dose has been over 60% in eligible MSM. To establish a baseline prevalence of HPV and to assess the impact of the vaccine, rectal swabs from men were tested and typed for HPV before and one year after the introduction of the programme.

Methods: Residual rectal swabs were taken from men in a city centre based sexual health clinic in Scotland which covers a large population. Swabs were taken from men who attended for a sexual health screen or for treatment and were tested for HPV pre- (n= 1209) and post-introduction (n= 1235) of the HPV vaccination programme. Vaccination status was not known and indication for a rectal swab was used as a proxy for MSM behaviour. HPV type prevalence, specifically HPV types 6, 11, 16 & 18, was compared before and after the introduction of the vaccination programme.

Results: Demographics of the baseline and post vaccine samples were similar and comparable (median age 33 years for both samples). Any HPV prevalence was higher in rectal swabs after the introduction of the HPV vaccine with 79.5% (95% CI 77.1-81.7%) positive for any HPV type compared to 72.8% (95% CI 70.1-75.2%) of baseline samples. Positivity for at least one HPV type present in the quadrivalent vaccine was 49.5% (95% CI 46.6-52.4%) at baseline and 47.4% (95%CI 44.6-50.2) after the introduction of the vaccine. HPV 16/18 prevalence decreased from 37.9% (95%CI 35.2-40.8%) to 31.8% (95% CI 29.2-34.5%) and when restricted to those aged ≤45 years, HPV 16/18 prevalence decreased from 37.7% (95% CI 34.5-40.9%) in the baseline sample to 31.2 (95% CI 28.3-34.2%). Rectal swabs in the post vaccine sample had significantly decreased odds of being positive for HPV 16/18 compared to the pre-vaccine group (OR 0.76, 95% CI 0.64-0.90 (p=0.0014)) which remains significant when restricting to samples from those aged ≤45 years (OR 0.75, 95% CI 0.63-0.91 (p=0.003).

Conclusions: While overall HPV prevalence was higher in rectal swabs taken after the introduction of the vaccine, prevalence of HPV 16/18 was significantly decreased in post vaccine swabs compared to swabs taken before the vaccine was introduced. This decrease may represent the first indication of the beneficial effect of the HPV vaccine on high-risk vaccine type HPV prevalence in MSM which should translate to a reduction in disease in subsequent years. Future sampling of rectal swabs should further strengthen our conclusions.

FC 08 - HPV prophylactic vaccines (II)

#0086

34 - Economics and modelling

Impact and Cost-effectiveness of Adopting WHO Recommendations on Cervical Cancer Elimination in the United States

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Background/Objectives: In May 2018, the World Health Organization (WHO) Director-General made a global call for action towards the elimination of cervical cancer (CC) as a public health problem, which will involve setting ambitious screening and vaccination coverage targets. The draft WHO strategic plan for elimination proposes a CC incidence target of 4/100,000 women per annum. We performed a comparative modeling analysis using two models from the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to explore the timing and value of adopting CC control targets outlined by the WHO in the USA, as well as potential other targets.

Methods: We used two independently-developed CISNET models (Harvard and Policy1-Cervix) to estimate the health benefits (e.g., incidence rates) and economic consequences associated with nine alternative CC prevention scale-up scenarios compared with a "status quo' scenario that involved no additional interventions. Both models involved a dynamic multicohort-modeling platform to capture changes in health outcomes over time, including herd effects. Sensitivity analysis explored the impact of alternative standard population structures, inter alia.

Results: Under status quo assumptions, both models projected that CC incidence would fall below 4/100,000 women by 2045 (with <5 years between model predictions). Sensitivity analysis using different population structures generated a range of approximately +/- 10 years around these predictions. Scaling-up screening coverage to 90% was the most impactful intervention in terms of relative cancer reductions, averting between 11% (CCNSW) and 19% (Harvard) additional cases over 2020-2100. Although increasing female vaccination coverage to 90% was considered high-value, the decrease in CC burden was lower than increasing screening coverage. Scaling up vaccination coverage of boys to 90% or vaccinating adults aged 26-45 years were identified as low-value interventions.

Conclusions: Under status quo assumptions, both Harvard and Policy1-Cervix found that national CC rates may fall below 4/100,000 women by 2045, and may be expedited if improvements in screening coverage are achieved. Both models reached consensus about low-value interventions. These national estimates do not apply to all subgroups of women; therefore, reaching under-screened and under-vaccinated women remain key to achieving CC elimination for all women.

#0344

5 - HPV prophylactic vaccines

BURDEN OF HPV RELATED ANOGENITAL DISEASES IN YOUNG WOMEN IN GERMANY - AN ANALYSIS OF GERMAN STATUTORY HEALTH INSURANCE CLAIMS DATA FROM 2012 - 2017

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Background/Objectives: In 2007 the German Standing Committee on Vaccination (STIKO) released the first HPV vaccination recommendation for girls. In the first year after the introduction, HPV vaccination rate was reported with 32% for at least one dose in 12 to 17 years old girls. In 2015, HPV vaccination rate was 31% in 15 years old and 45% in 17 years old girls (3 doses). The aim of this study was to evaluate the burden of potentially HPV-related anogenital diseases in young women in years following introduction of HPV vaccination.

Methods: We conducted a retrospective claims data analysis using the Institute for Applied Health Research Berlin (InGef) research database. The InGef research database contains claims data of approximately 4 million insured individuals and is adjusted by age and gender to the German overall population. In the period from 2012-2017, all women from birth cohorts 1989-1992 were identified if they were continuously insured at the age of 23-25. Women were included who were too old (birth cohort 1989) for HPV vaccination as well as women who were eligible for HPV vaccination according to STIKO recommendation (birth cohorts 1990-1992). Using ICD-10-GM codes, the administrative prevalence (95% confidence interval) of genital warts, anogenital dysplasia grade I, grade II and grade III was calculated. Since cervical cancer screening is recommended in Germany starting at the age of 20, most records of dysplasia most likely resulted from routine screening (cytology) and further work-up (histology). No information on HPV vaccination status was available.

Results: From 2012-2017 a total of 15,358 (birth cohort 1989), 16,027 (birth cohort 1990), 14,748 (birth cohort 1991) and 14,862 (birth cohort 1992) women at the age of 23-25 were continuously insured. 5.52% (5.16-5.89; birth cohort 1989) and 4.47% (4.15-4.82; birth cohort 1992) of the women had at least one record of the analyzed ICD-10-GM diagnoses. A decrease in the administrative prevalence was observed for genital warts (1.30% (1.12-1.49) birth cohort 1989 vs. 0.94% (0.79-1.10) birth cohort 1992) and dysplasia grade III (1.09% (0.93-1.26) birth cohort 1989 vs. 0.71% (0.58-0.86) birth cohort 1992). For dysplasia grade III, this trend was most evidently observed for severe cervical dysplasia (0.91% (0.76-1.07) birth cohort 1989 vs. 0.60% (0.48-0.74) birth cohort 1992).

Conclusions: A decrease of the burden of genital warts and anogenital diseases grade III was observed in the younger birth cohorts that were eligible for HPV vaccination according to STIKO. Further research is necessary to confirm the observed trend, including analyses linked to vaccination status.

#0439

5 - HPV prophylactic vaccines

LONG-TERM EFFECTIVENESS OF THE 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE IN SCANDINAVIAN COUNTRIES

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Background/Objectives: A long-term follow-up (LTFU) extension (NCT02653118) of the pivotal efficacy study of the 9-valent human papillomavirus (9vHPV) vaccine in young women 16-26 years of age (NCT00543543) was initiated to assess effectiveness for up to 14 years total follow-up (approximately 4 years in the base study; 10 years in the LTFU study). We report data from an interim analysis conducted at 8 years post-vaccination.

Methods: Participants from Denmark, Norway, and Sweden, who received 9vHPV vaccine during the base study and provided consent, continued into the LTFU study. National health registries were used to assess those attending screening and diagnosed with cervical precancers and cancers. Tissues from histological confirmation of cervical pathology (biopsy and definitive therapy) were retrieved to be analyzed by polymerase chain reaction to detect HPV DNA and for pathology diagnosis adjudication. To assess effectiveness, the observed incidence of HPV16/18/31/33/45/52/58-related cervical intraepithelial neoplasia-2 (CIN2), CIN3, adenocarcinoma in situ (AIS), or cervical cancer ("CIN2 or worse") was compared with the estimated incidence rate in an unvaccinated cohort of similar age and risk level using a control chart method. Primary effectiveness analyses were conducted in the per-protocol effectiveness (PPE) population.

Results: Of 2223 participants from Denmark, Norway, or Sweden who received at least 1 dose of 9vHPV vaccine at the start of the base study, 2029 continued into the LTFU study. Among participants included in the PPE analyses (n=1799), the median effectiveness follow-up post-Dose 1 was 6.8 years (range: 0.5, 10.0). During the LTFU study period, among 1448 PPE population-eligible participants contributing 4084.2 person-years follow-up, no new cases of HPV16/18/31/33/45/52/58-related CIN2 or worse were observed as of the data cut-off date (Jan 1, 2018). Over at least 6 years of total follow-up post-9vHPV vaccine Dose 1, there were no signals observed in the control chart analysis that indicated waning of vaccine effectiveness in the PPE population.

Conclusions: The 9vHPV vaccine provides continued protection through at least 6 years following vaccination with a trend toward continued effectiveness for up to 8 years.

#0413

5 - HPV prophylactic vaccines

INFECTION WITH MULTIPLE HUMAN PAPILLOMAVIRUS TYPES IN UNVACCINATED AND VACCINATED 17-YEAR-OLD NORWEGIAN GIRLS

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Background/Objectives: Women with a human papillomavirus (HPV) infection are often infected with more than one HPV type. Potential interactions between HPV types may impact the effectiveness of HPV vaccination programs. However, whether infection with one type may directly reduce or increase the risk of infections with other types is not known. We studied the occurrence of concurrent HPV infections among both vaccinated and unvaccinated 17-year-old Norwegian girls.

Methods: Urine samples were collected from the first birth cohort of girls offered the HPV vaccine through the Norwegian Immunization Program (born in 1997) and from one birth cohort not eligible for vaccination (born in 1994). The samples were tested for 37 HPV genotypes using a modified general GP5+/GP6+ polymerase chain reaction protocol followed by a Luminex-based genotyping test. Individual records of HPV vaccination were obtained through linkage with the Norwegian Immunization Registry. Mixed-effect logistic regression with an individual-level random intercept was used to model risk of HPV infection in order to account for dependencies between infections due to subject-specific factors. The analyses were restricted to unvaccinated girls born in 1994 (n = 5245) and vaccinated girls born in 1997 (n = 5039). Expected frequencies of concurrent infection with all 91 possible pairwise combinations of the vaccine types and high-risk types (6/11/16/18/31/33/35/39/45/51/52/56/58/59) were calculated separately for each birth cohort.

Results: The number of girls infected with more than one HPV type was 481 (9.2%) in the 1994-cohort and 187 (3.7%) in the 1997-cohort, corresponding to 50.3% and 35.4%, respectively, of girls with HPV-infection. Concurrent infection with the following HPV-types occurred significantly more often than expected in the 1994-cohort: 16+52 (p=0.049), 18+51 (p=0.02), 31+52 (p=0.005), 33+51 (p=0.002), 39+45 (p=0.04), 39+52 (p=0.02), 39+58 (p=0.03), 45+59 (p=0.02). In the 1997-cohort, the pairs that occurred significantly more frequently than expected were 6+18 (p=0.04), 11+16 (p=0.049), 33+51 (p< 0.001), 33+58 (p=0.01), 39+56 (p=0.03). No pairs were observed significantly less often than expected in either cohort.

Conclusions: In both the unvaccinated and the vaccinated cohort,more girls than expected had concurrent infection with HPV33 and HPV51. Other findings were not consistent across birth cohorts. Thus, no clear evidence of interactions between any other types was found.

#0522

5 - HPV prophylactic vaccines

ANAL HPV PREVALENCE SOON AFTER IMPLEMENTATION OF PUBLICLY FUNDED VACCINE FOR GAY, BISEXUAL AND OTHER MEN WHO HAVE SEX WITH MEN: A CANADIAN IMMUNIZATION RESEARCH NETWORK-FUNDED STUDY

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Background/Objectives: Since 2015/16 in some Canadian provinces, HPV vaccine has been publicly funded for gay, bisexual, and other men who have sex with men (gbMSM) aged ≤26 years. Older men may access it via private insurance or out-of-pocket payment. We compared the prevalence of anal HPV between vaccinated and unvaccinated gbMSM soon after the implementation of these programs.

Methods: Self-identified gbMSM were recruited for the Engage Cohort Study using respondent-driven sampling (RDS) in Montreal, Toronto, and Vancouver, Canada. At enrollment, men aged 16-30 years self-collected anal specimens for type-specific HPV-DNA testing (36 genotypes) and self-reported HPV vaccination status. Outcomes: (1) any HPV type; (2) quadrivalent vaccine-preventable types (HPV6/11/16/18); (3) nonavalent vaccine-preventable types (HPV6/11/16/18/31/33/45/52/58); and (4) non-vaccine preventable types. RDS-unadjusted prevalence estimates were compared using Fisher's Exact test.

Results: Between 02/2017 and 02/2019, 485 gbMSM provided valid anal specimens for HPV-DNA testing. RDS-unadjusted vaccine uptake (at least 1 dose) was 39.6% overall (50.0% in 16-26-year-olds and 27.0% in 27-30-year-olds). Among vaccinated men, 60.6% had received 3 doses. Vaccinated men reported more sexual partners in the past 6 months (mean=8) than non-vaccinated men (mean=5; p=0.002 Wilcoxon signed-rank test). Anal prevalence for any HPV type was 69.5% overall. For quadrivalent vaccine-preventable types, prevalence was lower in vaccinated compared to unvaccinated men (21.1% vs. 27.7%; standardized difference [SD]=−15.5%; p=0.122). This pattern was less pronounced for nonavalent types (32.2% vs. 35.0%; standardized difference [SD]=−6.0%; p=0.545). Differences were largely driven by HPV11 (1.7% vs. 7.7%; SD=−28.7%; p=0.005) rather than by HPV16 (9.4% vs. 10.9%; SD=−5.0%; p=0.640), HPV6 (9.4% vs. 10.2%; SD=−2.6%; p=0.873), or HPV18 (5.6% vs. 4.0%; SD=7.2%; p=0.497). Conversely, non-vaccine-preventable types other than 6/11/16/18 were more common in vaccinated than unvaccinated men (65.6% vs. 58.4%; SD=14.8%; p=0.140) as was any HPV type (71.1% vs. 67.2%; SD=8.6; p=0.408).

Conclusions: Among gbMSM aged 16-30 years in the largest cities in Canada, vaccinated men were younger and reported more recent sex partners. Although imprecise, point estimates of anal prevalence were higher among vaccinated men for any HPV type and for non-quadrivalent-vaccine-preventable types, but lower for vaccine-preventable types. Population-level estimates of vaccine protection among young gbMSM may be confounded by age or sexual exposure. Ongoing monitoring of effectiveness is needed in this high-risk population.

#0337

5 - HPV prophylactic vaccines

NO HPV 6/11/16/18 INFECTIONS UP TO 10 YEARS AFTER VACCINATION OF 9-11 YEAR-OLD GIRLS WITH 2-DOSES OF QUADRIVALENT VACCINE

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Background/Objectives: The Province of Québec, Canada, initiated a school-based HPV vaccination program in 2008 and since its inception has used two doses of HPV vaccine in grade 4 at a 6-month interval. As part of the program evaluation, the ICI-VPH study was initiated in 2013. The main objective of ICI-VPH is to evaluate whether a 2-dose schedule (0, 6 months) of quadrivalent vaccine (4vHPV) is non-inferior to a 3-dose schedule (0, 6, 60 months) of the same vaccine for prevention of persistent HPV16 and 18 infections, 10 years after the first dose administration. As the 2-dose schedule is being increasingly adopted internationally for vaccinating pre-teens and teens, essentially based on immunobridging data, we thought timely to analyze and present interim virology results from the 2-dose group of ICI-VPH.

Methods: Between 2013 and 2016, we recruited girls who had been vaccinated with 2 doses of 4vHPV in grade 4 (9-11 years old), in 2008, 2009, 2010 and 2011. The participants were randomly assigned (1:1) to receive or not a 3rd dose of 4vHPV. Participants self-collect a vaginal sample every 6 months. Our primary outcome being persistent infections, we test every second vaginal sample (i.e. samples from even number time points, representing testing on a yearly base) for HPV DNA (generic test and Linear Array) and when positive, we test the previous and subsequent samples, to determine if the infection is transient or persisted at least 6 months. Participants also provide health and behavior data every year by completing an online questionnaire.

Results: A total of 1675 13-16-year-old girls were randomly assigned to the 2-dose group of the ICI-VPH study. Of those, 1612 participants (96%) were still active in follow-up by August 2019, and by then were 6 to 10 years from their first dose of 4vHPV. Participants were 16-20 years old and 66% of them declared being sexually active. Vaginal samples were available for 1611 girls. Among the 4812 samples tested at even number time points, no sample was positive for HPV 6/11/16/18 DNA. At 6, 7, 8, 9 and 10 years post first dose of 4vHPV, 2%, 6%, 12%, 22% and 36% of the samples tested were positive for at least one HPV type not targeted by the 4vHPV, respectively. Overall, the most frequently detected high-risk HPV were types 39/51/52/56/59 and low-risk HPV were types 42/84/89.

Conclusions: Six to 10 years post first dose of 4vHPV, no vaccine targeted HPV types (6/11/16/18) were detected among 1611 girls immunized at the age of 9-11 years with two doses of 4vHPV vaccine at a 6-month interval and included in the 2-dose group of the ICI-VPH study. The study is ongoing and will generate data up to 13 years after the initiation of vaccination.

#0163

5 - HPV prophylactic vaccines

Effectiveness of HPV vaccination against invasive cervical cancer

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Background/Objectives: In Sweden, HPV vaccines to prevent cervical cancer were made available in late 2006 and in 2007. The vaccine was initially subsidized for women age 13-17 years and coverage reached about 50%.Starting in 2012 a school based, organized HPV vaccination program for girls aged 10-12 years was launched free of charge, together with a catch-up program for women aged 13-18 years, which varied in delivery strategy. Vaccination coverage for subsidized HPV vaccination reached around 25-30% of the target group, and 50-60% for the catch-up program, while coverage for the school based HPV vaccination reached 80-84%. Gardasil has been used almost exclusively in Sweden. Several studies have investigated the population effectiveness of Gardasil against genital warts and CIN 2/3 with promising results; however, no study to date has investigated the effectiveness of HPV vaccination against invasive cervical cancer, the ultimate target of the HPV vaccination program. We here present the first results estimating relative risks of HPV vaccination against invasive cervical cancer.

Methods: Utilizing Swedish data on registration of HPV vaccination and cervical cancer from the national Swedish Cancer Registry during 2006-2017 we investigated the effectiveness of HPV vaccination against invasive cervical cancer in a national cohort study of 1,427,619 women aged 15-30. The Swedish population register was utilized to identify the underlying population at risk. Calculation of time-at-risk and number of cases for HPV vaccinated and unvaccinated women, respectively, with HPV vaccination as a time-varying exposure was done to estimate the incidence rate of cervical cancer up to age 31. Parental characteristics including mother's country of birth, highest achieved parental educational level, annual family income level, mother's disease history, and mother's county of residence were retrieved from corresponding national registers. Incidence rate ratios (IRR) of invasive cervical cancer, with 95% confidence intervals (CI), were estimated in Poisson regression models, controlling for attained age as a spline term, birth cohort in 5-year categories, and several parental characteristics.

Results: A total of 383,694 women (26.9%) had at least one dose of HPV vaccination, and 1,043,925 (73.1%) women were unvaccinated.During the study period 19 HPV vaccinated women acquired cervical cancer before age 31, while the corresponding number for unvaccinated women was 538, yielding an incidence rate of 1.00 and 6.51 per 100 000 person-years, respectively. The IRR for HPV vaccinated vs. unvaccinated women was 0.50 (CI:0.32-0.80) after adjusting for age, 0.38 (CI:0.24-0.62) after additional adjustment for birth cohort, and 0.37 (CI:0.23-0.60) with additional adjustment for parental characteristics. The IRR for women vaccinated before age 17 and age 17-30 were 0.12 (0.03 - 0.49) and 0.48 (0.29 - 0.79), respectively, after adjusting for all covariates. For women vaccinated before age 20 the IRR was 0.35 (CI:0.19-0.65), and for women vaccinated age 20-30 the IRR was 0.41 (CI:0.19-0.86).

Conclusions: These results indicate that HPV vaccination is effective against cervical cancer on the population level and that young age at vaccination is a strong mediator of vaccine effectiveness.

#0225

5 - HPV prophylactic vaccines

Study of the impact of catch-up vaccination against papilloma virus on high-grade cervical dysplasia in France

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Background/Objectives: Cervical cancer is the 11th leading cause of cancer death in France. Human Papilloma Virus (HPV) are the main agents responsible for this disease. For the past 12 years, two vaccines have been available to prevent HPV infection and the development of precancerous lesions and cervical cancer. Population-based studies showed a reduced risk of cervical dysplasia in vaccinated young women in other countries. In case of high-grade cervical dysplasia, a surgical procedure by conization is the standard treatment, with potential impact on further pregnancies. We present here, the first results of the impact of catch-up vaccination on conization in France in a population based study.

Methods: We conducted a retrospective real-life cohort study on data collected prospectively by French National Health Insurance. Data collected prospectively and permanently included the demographic and care data of 1/97th of the French population. We extracted data from all women born between 1984 and 1991, corresponding to the catch-up population only at time of HPV vaccine implementation. We compared the conization rate between vaccinated and not vaccinated young women.

Results: The cohort consisted in 42 452 women. Vaccination coverage (at least one dose) was 9.8%. The coverage rate increased with time from vaccine implementation, from 0.5% in the 1984 cohort to 31% for the 1991 cohort. The conization rate was 1% for the entire cohort. The risk of conization between 19 and 30 years-old was reduced in the vaccinated group with a Hazard Ratio (HR) of 0.59 (95% CI[0.39-0.90]; p=0.043).

Conclusions: With a 10-year follow-up, HPV vaccination in catch-up population reduces the risk of conization between the ages of 19 and 30.

#0367

5 - HPV prophylactic vaccines

HPV vaccine against CIN3+ is also highly effective in Japan, but still suspended

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Background/Objectives: An interim vaccination program (Emergent vaccine promotion program) against HPV started in Japan in November 2010 for girls aged 12-16 years, and it was included in the National immunization program in April 2013. In June 2013, however, the Ministry of Health, Labor, and Welfare suspended proactive recommendations for HPV vaccine after unconfirmed reports of adverse events in the media. From 70-80% coverage of girls' vaccination (at least one dose in a three-dose regime) during the first years of the interim program (birth cohorts in 1996-1999) and thereafter are consistently poorly vaccinated (0.01%, birth cohort in 2004), due to unproven suspicions of vaccine-induced side effects (1). In our earlier study, the vaccine effectiveness against CIN2+ was 71% (2). Because national data surveillance is immature and is not organized, linkage with other databases related to screening programs such as a regional cancer registry, laboratory files, and treatment files is not possible in Japan.

Methods: We collected the matched data of the results of cervical biopsy and history of vaccination from the database of the biggest cancer screening organization in Japan. The subjects were women aged 20 to 29 years screened for cervical cancer between April, 2015 and March, 2017, and with information on HPV vaccination status. We estimated the relative risk of developing high-grade cervical lesions in a vaccinated group using Poisson regression as compared to an unvaccinated group.

Results: Among the 34,281 women screened, 3,770 (11.0%) were vaccinated. The prevalence of CIN2+ was significant lower in the vaccinated women as compared to the unvaccinated women (Vaccine Effectiveness (VE) =76%; RR=0.24, 95% CI:0.10-0.60). High VE against CIN3+ was also observed (91%; RR=0.09, 95% CI:0.00-0.42).

Conclusions: Lessons learned from HPV vaccine concerns are that surveillance with a well-designed registry system is necessary, and risk communication based on epidemiology is important to maintain the national health policy. Limited scientific investment in cancer prevention and the absence of scientific renovation has caused serious problems. On the other hand, HPV vaccine effectiveness was shown more robustly in this report. Japan needs to issue strong recommendations for the HPV vaccine and HPV-based cervical cancer screening based on scientific evidences to break the stigma. Otherwise, Japan is likely to continue witnessing increased incidence and mortality rates.

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FC 09 - HPV prophylactic vaccines (III)

#0361

5 - HPV prophylactic vaccines

The impact of prophylactic vaccination on HPV elimination in women after surgical treatment of HSIL.

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Background/Objectives: Persistent infection with HPV oncogenic types in patients after surgery due to histopathological HSIL is a great challenge for every doctor. This problem can also have a very negative impact on the quality of patients' life, being a high psychological burden. Doctors treating such patients, apart from cytological and molecular diagnostics, can not offer alternative effective treatment options of human papillomavirus infection. In order to meet patients' expectations, the use of prophylactic HPV vaccines was suggested. Each patient was informed that there is no evidence of the benefits of this type of treatment and that the vaccine is not therapeutic.

Methods: 27 patients diagnosed with histopathological HSIL changes and a HPV positive test result for oncogenic types were qualified for the study. All patients underwent surgical treatment consisting of removal of HSIL changes from the cervix. Histopathological examination confirmed complete removal of the lesion. During post-treatment follow-up, patients underwent cytological and molecular tests for the presence of oncogenic HPV types. Patients with persistent infection with HPV oncogenic types were qualified for the prophylactic vaccine. Three doses of the vaccine were provided in a cycle of 0, 2, 6 months. Six to 12 months after the last dose of vaccine, a molecular test for HPV was performed.

Results: Of 27 patients included in the study, 26 had negative molecular test results while one patient was still positive. After genotyping, the patient turned out to be infected with HPV type 68.

Conclusions: As the vaccine has a preventive and not therapeutic profile, the mechanism of action affecting the elimination of HPV cannot be clearly explained. It cannot be excluded that the elimination of viruses follows the healing processes after the patient's surgical procedures. The results of the presented study indicating a very high virus elimination rate have been used as a pilot study to design a new study. The study included patients with HPV HR infection 6 months persistent following HSIL treatment. For the actual assessment of the impact of preventive vaccination on the dynamics of HPV elimination in the new study, patients are randomly classified into 2 groups. The first group, which receives the nine-valent vaccine and the second group, have only cytological and molecular tests performed. The authors hope that the obtained results will answer the question whether prophylactic vaccination in the group of HSIL women with persistent HPV HR infection contributes to faster HPV elimination.

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#0087

6 - HPV therapeutic vaccines

Effectiveness of HPV vaccine in women undergoing LEEP for cervical dysplasia

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Background/Objectives: It was estimated that ~570,000 women developed cervical cancer and 260,000 died in 2018. Human PapillomavirusVirus (HPV) infection is associated with the occurrence of pre-malignant and malignant cervical lesions, whose clinical burden have been affected by the implementation of national vaccination programs, early diagnosis, and evidence-based clinical management. A high (5%-10%) 2-year risk of recurrence was shown in patients who underwent a surgical intervention for cervical dysplasia. Aim of the present study was to evaluate the recurrence rate in patients immunized with HPV vaccine one month before/after a loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN1-3).

Methods: An observational retrospective, mono-center study was carried out, enrolling women with a diagnosis of cervicaldysplasia and treated with a LEEP between January 2012 and October 2018in the University Hospital of Sassari, Italy. Only285/503(56.7%) were considered suitable because of a follow-up of >24 months. HPV vaccination was voluntarily offered to patients according to the national immunization program

Results: 182 (63.9%) and 103 (36.1%) women were and were not vaccinated, respectively. Patients immunized with HPV vaccine were significantly younger (median [IQR]: 41 [36-49] VS. 37.5 [30-45] years; p-value: 0.0004). Proportion of positivity of margins of resection were not different between the recruited groups. Recurrence was diagnosed in 30(13.3%) women: 17 (16.5%) and 13 (7.1%) were vaccinated and not vaccinated (p-value=0.01), respectively. Cervical recurrences were severe (CIN2/3) (19/30, 63.3%) in the majority of the cases. HPV vaccination was the only protective covariate for cervical recurrence (OR: 0.4; p-value: 0.02).

Conclusions: Administration of HPV vaccine immediately before or after LEEP significantly reduced the risk of recurrence by ~60%. Based on its observational nature, confounding factors (e.g., severity of the lesions at baseline, 2/4-valent HPV vaccine, HPV genotype, comorbidities, etc.) could have biased the results. Experimental, randomized, studies, based on restrictive selection criteria, could better evaluate the preventative role of HPV vaccines in surgically-treated patients.

#0525

5 - HPV prophylactic vaccines

REDUCTION IN CIN3+ AT SECOND AND SUBSEQUENT SCREENS IN WOMEN IMMUNISED WITH CERVARIX®

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Background/Objectives: In 2008, Scotland implemented hr-HPV immunisation with bivalent vaccine at age 12/13 for women born in and after 1995 and catch-up immunisation for women born during 1990-1994. Women in the catch-up cohort have been screened since 2010, and routinely immunised women since 2015. Women born before 1994 have had two screening opportunities over 6 years and routinely immunised women have had a minimum follow-up of 3 years. We have presented data showing that immunisation reduces disease significantly at second screen at age 23-25 years in the catch-up cohorts. We now report on both routinely-immunised women and the catch-up cohorts.

Methods: Immunisation status, cervical cytology and histology results were retrieved in July 2019 from the Scottish National Screening database for all women born between 1 January 1988 and 6 June 1996. Women born in 1988-1990 are largely un-immunised, women born in 1991-1994 are the catch-up cohort, and those born in 1995-1996 are routinely immunised. The rates of CIN3+ have been calculated.

Results: A total of 437,583 individual patient records were examined. 262820 have had cytology. A total of 4454 CIN3+ events have been recorded during follow-up (Table). 1271 CIN3+ events have been recorded at ages 20-23 years in all cohorts. The risk reduction relative to the cohort not offered vaccination is 51.8% (95% CI 45.6%, 56.9%) in the catch-up cohort and 89.6% (85.5%, 92.6%) in routine cohort. The risk reduction within the catch-up cohort for immunised relative to non-immunised women is 27.2% (13.6%, 38.7%). 2833 CIN3+ events have been recorded in women in the unvaccinated and catch-up cohorts with at least 6 years follow-up. Within the catch-up cohorts the risk of CIN3+ in immunised women relative to non-immunised women was reduced by 29.7% (CI 20.6 - 37.8%). The CIN3+ totals include 76 invasive cancers. Women in the routine vaccination cohort (1995-96) have a maximum follow up of 4 years and 21 cancers have been observed at age 20-24 in all cohorts, 11 in the cohort not offered vaccination (rate 0.96/106); 10 in the catch-up cohort, (rate 1.07/106) and 0 in the routine cohort. In the catch-up cohort the rate of cancers among those fully vaccinated is 0.72/106 while among those unvaccinated the rate is 1.49/106. Number and Rate of CIN3+ cases in women at second and subsequent screens Age band/ duration of follow-up Number and Rate CIN3+ per 100,000 person years Not offered vaccination Catch-up vaccination Routine vaccination Not immunised 3 doses 20-23 3 years 710/70.6 525/51.4 36/19.5 274/58.7 251/45.3 >= 26 6 years 1792/179 1041/123 583/143 458/104

Conclusions: Significant reductions in CIN3+ in both routinely immunised and catch-up cohorts is demonstrated over several screening rounds. Although there is a reduction in cancers in immunised women the numbers are too small and follow-up of routinely immunised women too short for definitive results. The reduction in CIN3+ gives confidence that the predicted reduction in invasive cancers will be seen.

#0421

5 - HPV prophylactic vaccines

HPV VACCINATION AFTER CONIZATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background/Objectives: Over the last decade HPV vaccination has become a fundamental part of prevention of cervical cancer and cervical intraepithelial neoplasia (CIN). The aim of prevention is to vaccine before the patient's first contact to the virus. Recent studies have shown that the progression from HPV infection to precancer cannot be stopped by HPV vaccination. After excisional treatment of high-grade CIN women still have an elevated risk to develop invasive cervical cancer. Therefore, a long-term reduction of this risk is important and pre- and post-conization HPV vaccination could be a possible way to achieve this.

Methods: In this meta-analysis, six pro- and retrospective studies analysing the effect of pre- or post-conization vaccination (bi- or quadrivalent vaccine) against HPV were included after a systematic review of literature. Fixed- and random-effect models were prepared.

Results: Primary end point was CIN2+ in every study. The total study population included 3060 patients (1427 vaccinations vs 1633 controls) in six studies. The meta-analysis showed a significant reduction of risk for the development of new high-grade CIN after HPV vaccination (risk rate (RR) 0.33; 95% CI [0.21; 0.52]), independent from HPV type. Due to the heterogeneous study population, multiple meta-analyses regarding the HPV type, age of patient, time of vaccination and follow-up were performed. Results for HPV 16 and 18-positive CIN2+ showed a RR of 0.41 (95% CI [0.2; 0.85]. Discrimination between younger women (age 18-26) and women of all age (age 18-45) revealed a risk rate of 0.4; 95% CI [0.21; 0.76] and 0.28; 95% CI [0.15; 0.53], respectively. After a longer period of time after vaccination (median follow-up time > three years), the relative risk was 0.33; 95%-CI [0.19; 0.59], whereas the risk for CIN2+ after a maximum time of three years of follow-up was 0.32; 95% CI [0.15; 0.69]. The relative risk of vaccination before and after operative therapy was 0.31; 95% CI [0.15; 0.65] and 0.34; 95% CI [0.19; 0.61], respectively.

Conclusions: Meta-analysis and subgroup analyses showed a significant risk reduction of developing high-grade cervical intraepithelial neoplasia after HPV vaccination and surgical excision.

#0187

34 - Economics and modelling

HEALTHCARE RESOURCE UTILIZATION AFTER CERVICAL CONIZATION: 2 YEAR FOLLOW-UP FROM A LARGE UNITED STATES CLAIMS DATABASE

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Background/Objectives: Human papillomavirus (HPV) infection of the cervix can lead to the development of cervical intraepithelial neoplasia 2/3 (CIN2/3), and eventually cervical cancer; this infection can be prevented through nonavalent HPV vaccination. Screen-detected CIN2/3 can be treated by cervical conization, but patients undergoing conization often experience recurrence within 2 years. Our objective was to estimate the post-conization healthcare resource utilization (HCRU) to inform estimates of the overall burden of CIN2/3.

Methods: We conducted a retrospective cohort study using the Truven MarketScan® database, a large healthcare claims database in the US. Females between the age 18-45 at the time of first conization procedure between 2012 and 2015 were identified using CPT codes for conization (57522, 57520)/ ICD-9/10-PCS (ICD-9 67.2, ICD-10 0UBC7ZZ). We then estimated HCRU including frequency of tests, procedures, and diagnoses commonly associated with cervical HPV (Pap test, HPV test, colposcopy, biopsy, endocervical curettage (ECC), conization, hysterectomy, CIN2/3 and HPV infection) during the follow-up period.

Results: Of 15,817 patients meeting inclusion criteria, about 85% of women had at least one Pap test between 7-24 months post-conization. 50% women had at least one HPV test in 7-24 months after conization, with 9% women having a visit for HPV infection. About 15% women had at least one visit for CIN3 in the 7-24 month follow-up period. Colposcopy and ECC were the most common procedures. 3% had a second conization within 6 months.

Conclusions: HPV-related healthcare utilization continues for at least 2 years post-conization, including follow-up procedures and, potentially, recurrent infection (which could not be confirmed in a claims-based analysis). HPV vaccination should reduce the burden of CIN2/3, conization, and post-conization follow-up.

#0665

29 - HPV and oropharynx / Head and neck cancer

EFFICACY OF AS04-ADJUVANTED HPV-16/18 VACCINE IN REDUCING OROPHARYNGEAL HPV INFECTIONS IN ADOLESCENT GIRLS - RESULTS FROM A COMMUNITY-RANDOMIZED TRIAL**

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Background/Objectives: Aside from its causal association with cervical cancer, high-risk Human Papillomavirus (HPV) infections can lead to the development of oropharyngeal cancers. Over the last two decades, prevalence and incidence of high-risk HPV-positive oropharyngeal cancers in non-vaccinated populations has dramatically increased in affluent countries. Prophylactic HPV vaccines have already been shown to be highly efficacious in preventing persistent cervical infections and precancerous lesions associated with the most prevalent carcinogenic HPV types (HPV-16 and -18) and some related oncogenic HPV types. We present here secondary endpoint results of a phase III/IV, community-randomized, controlled study (NCT 00534638) evaluating vaccine efficacy (VE) of the AS04-adjuvanted HPV-16/18 vaccine (AS04-HPV-16/18) against oncogenic HPV oropharyngeal infections in adolescent girls.

Methods: From 2007 to 2010, 80,272 adolescents aged 12-15 years from 33 randomized communities in Finland were invited to participate in the study. 22,444 girls and 11,968 boys were allocated to 3 arms (A, B, C) of 11 communities each. Vaccinated subjects received either AS04-HPV-16/18 or hepatitis B virus (HBV) vaccine at months 0-1-6. Oropharyngeal samples were collected from girls born in 1994-95 after age 18.5 years and before age 19 years (5-6 years after vaccination). HPV DNA prevalence in the oropharyngeal samples was determined by SPF-10 line probe assay (LiPA) and Multiplex Type-specific PCR. VE was defined as a relative reduction of oropharyngeal HPV prevalence among HPV-vaccinated pooled-arms A and B girls compared to all HPV non-vaccinated girls from arm C (control arm).

Results: In arms A and B, 89.5% (8,235/9,203) of vaccinated girls and boys, and 89.6% (6,601/7,367) of vaccinated girls respectively, were blinded and received AS04-HPV-6/18. Other vaccinated participants in arms A and B (6,614) and all vaccinated subjects (10,724) in arm C received HBV vaccine. VE of AS04-HPV-16/18v against oropharyngeal infection with vaccine and other oncogenic HPV types in pooled arms A and B versus arm C, for birth cohorts 1994-95, using stratified Mantel-Haenszel adjusted for clustering (girls, total enrolled cohort). HPV type Arm N n VE (%) 95%CI (LL - UL) p-value 16/18 A & B 3,192 9 82.4 47.3 - 94.1 0.002 C 1,679 27 31/45 A & B 3,192 3 75.3 12.7 - 93.0 0.030 C 1,679 9 31/33/45 A & B 3,192 9 69.9 29.6 - 87.1 0.006 C 1,679 16 CI: confidence interval; LL: lower limit; N: number of subjects; n: number of positive samples; UL: upper limit; VE (%): vaccine efficacy (1-Odd Ratio)

Conclusions: AS04-HPV-16/18 shows evidence of high VE against oropharyngeal infections with vaccine HPV types (HPV-16/18) and other oncogenic HPV types (HPV-31/33/45) in adolescent girls vaccinated at the age of 12-15 years.

References: Funding: GlaxoSmithKline SA. * Authorship on behalf of the HPV-040 study group. ** This is an ENCORE abstract previously presented at EUROGIN 2017.

FC 10 - HVP screening (I)

#0561

9 - HPV screening

Risk of high-grade lesions after atypical glandular cells in cervical and HPV screening.

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Background/Objectives: To determine how high-risk (hr) HPV positivity of atypical glandular cells (AGC) affects the predictive values for presence of high-grade cervical lesions.

Methods: Between 2014-02-17 and 2017-06-30, there were 740 women with AGC in a cervical sample in the Stockholm-Gotland, Sweden region. Registry linkages identified that 540 women had an associated HPV test and a histopathological follow-up. Presence of high-grade cervical lesions in the cervical biopsies taken after the AGC diagnose, in relation to the HPV status of the AGC-containing index smear. Reflex HPV analyses were performed by the Cobas 4800 platform (Roche Diagnostic). A Population-based cohort study.

Results: The proportion of hr-HPV positive AGC was 61% (n=328). In this group, there were 10 cases of invasive cervical adenocarcinoma (ADCA), 56 cases of cervical adenocarcinoma in situ (AIS) and 128 cases of high grade squamous intraepithelial lesion (HSIL), giving a positive predictive value (PPV) for a cervical lesion to treat of 61% (201/328). Among the 212 (39%) women with HPV-negative AGC, there was 1 invasive cervical squamous cell cancer and 1 HSIL, giving a PPV for a cervical lesion to treat of 0.9%. This group also contained 7 endometrial cancers and 1 breast cancer. Findings of only HPV 18 positive samples is mainly associated with AIS / ADCA and HPV 16 samples can be observed more frequently in high-grade squamous epithelial changes, rather than adenomatous lesions. The other hr-HPV types mainly cause squamous epithelial lesions.

Conclusions: HPV defines AGC cases with an exceptionally high PPV for high-grade lesion to motivate follow-up. HPV triaging of AGC will greatly increase the predictive ability for cervical lesions to treat and the high sensitivity (96%; 132/137 women) implies safety of primary HPV screening strategies. The measurable risk for endometrial cancer among women with HPV-negative AGC suggests that research on screening for endometrial cancer is needed.

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#0486

9 - HPV screening

CANCER CASES IDENTIFIED IN A RANDOMIZED IMPLEMENTATION OF HVP SCREENING IN THE NORWEGIAN CERVICAL CANCER SCREENING PROGRAMME

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Background/Objectives: High risk Human Papilloma Virus (HPV) testing was implemented in a randomized controlled fashion as the primary screening test in the Norwegian Cervical Cancer Screening Programme in three counties in Norway from Febryary 2015 until April 2018. We present detailed evaluation of the cancer cases identified.

Methods: The implementation involves women in the age group 34-69 years in three Norwegian counties, counting approximately 285.000 women. In Norway, the follow-up algorithm after abnormal screening test has been more aggressive for HPV screening than for cytology screening, referring an increased number of women to direct biopsy, and potentially earlier detection of cancers. Cancer cases, symptomatic and screening detected, are identified for both women allocated to HPV test or cytology. An early concluding cohort, including women who have had time to complete the follow-up algorithm, was used for a more unbiased comparison of the cancer cases. Descriptive analyses of screening results (cytology/HPV status/genotype), screening history, symptoms, FIGO-stadium and age of the cancer-diagnosed women are presented.

Results: By April 2018, approximately 199.000 women have been screened, half with HPV test and half with cytology. Around 124.000 women have had time to have complete follow-up, and a total of 102 cancer cases are identified in the early concluding cohort; 63 cases belonged to the cohort allocated to HPV testing (49 squamous cell carcinoma, 12 adenocarcinoma, 1 other cervical cancer type) and 39 to the cohort screened by cytology (30 squamous cell carcinoma, 7 adenocarcinoma, 2 other cervical cancer type). Majority of the cancers are diagnosed after the index test suggested referral to colposcopy and direct biopsy. More than 60% of the women diagnosed with cancer are under-screeners/non-screeners. Around 75% of the cancers were related to HPV16 and HPV18, and the majority of the cancers were FIGO stadium I. Updated results will be presented.

Conclusions: Most cancer cases identified in the enrolment represent undiscovered premalignant lesions of previous screening rounds, and the actual number of cancer cases should be comparable between the two groups. Our early concluding cohort show a slight increase in the number of diagnosed cancer cases after primary HPV test, and the number of diagnosed cases should be followed closely.

#0546

34 - Economics and modelling

Using Population-Level Cervical Cancer Screening data to develop personalised screening algorithms

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Background/Objectives: The Cancer Registry of Norway has been administrating a triannual cervical cancer screening program since 1995 which target women 25-69 years of age. The guidelines recommend that each woman should attend to screening 16 times during her life-course. However, about 50% of guideline based screened women experience only normal screening tests. There is a need to develop optimal screening strategy to reduce over-screening, overuse of screening infrastructure, human resources and community outreach.

Methods: Information on cervical cancer screening, cytology, histology and HPV-test results are systematically collected by the Norwegian cervical cancer screening program since 1991. A dataset of about 10 million serial exams for 1.7 million women was used to simultaneously estimate all transition parameters in continuous-time, time-inhomogeneous hidden Markov model reflecting cervical cancer carcinogenesis and the screening process. The model was validated by simulating a synthetic dataset from the Markov model, and Kaplan-Meier estimators were used to compare the synthetic data with a real-world data set not used in the model estimation.

Results: The transition parameters estimated in the model were similar to estimates found in other studies. Intensities for progression from normal to low-risk stage was five times more common, and regression from high-risk to low-risk stage was four times more common in younger women compared to women at age 60+ years. Progression intensities from low-risk to high-risk were homogenous through the age-groups. Overall, the observed progression had a linear pattern, stretching over a decade, while regression occurred within a shorter period of 2-3 years. Of 16-19 years old women with exam suggesting normal stage, more than 20% had a low-risk exam in 10 years of follow-up. This proportion become gradually smaller with increasing age, reaching to 5% among women 60+ years of age. The same pattern was present when observing progression from normal to high-risk, but at lesser magnitude.

Conclusions: Our model has a potential to improve strategies for cancer screening programs by personalizing recommended screening intervals.

#0352

9 - HPV screening

Evaluation of population-based primary HPV cervical screening: 3 years after implementation

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Background/Objectives: National screening program has been ongoing in large parts of Sweden since 1966, and has led to a significant decrease in cervical cancer cases in Sweden (1, 2). Primary cervical screening with HPV for women between 30-70 years is recommended in Sweden by the National Board of Health and Welfare since 2015 (3). In the Region of Örebro County primary HPV screening with an mRNA assay was introduced in September 2016, where HPV positive cases are further analyzed with cytology as a triage. The aim of this study was to audit data of implemented organized primary HPV screening to determine the hrHPV prevalence in the screening-population, compare the sensitivity and specificity to detect HSIL between HPV screening and the former cytology based screening program and finally to determine the number of visits for follow-up with cervical-cell samples, colposcopy or treatment. All to evaluate the actual cost and effectiveness of the implemented HPV screening program.

Methods: The Region of Örebro County invites women every 3-5 years for cervical cancer screening (5 years for women over 50). The present audit was registry based where data from the Swedish National Cervical Screening Registry were matched to the local registries to determine HPV status, cytology and histology diagnoses, and number of visits for sampling, colposcopy and surgical treatments. Data from cytology based screening 2014 to August 31, 2016 was compared to data with mRNA HPV primary screening from September 1st, 2016 through 2018.

Results: This audit evaluates organized primary HPV screening implemented 3 years ago in the Region of Örebro County, Sweden. With primary HPV test, the prevalence of HPV was 7% (2316/32938), with cytological abnormalities in 47% of the samples that needed follow-up. Thus 3,3% (1090/32938) of the total number of primary HPV tested samples were HPV positive and cytology positive results, compared to the primary cytology screened samples that had abnormal cytology in 5,7% (1632/28725) of the cases, including both low and high-grade abnormalities.

Conclusions: Further results will be presented at the conference comparing implemented primary HPV screening with mRNA to former cytology screening, with focus on histological outcomes, number and types of follow-up visits leading to histological findings or HPV clearance/cytological normal samples.

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#0504

9 - HPV screening

Registry-based comparison of cervical screening test results in the Nordic countries by test method

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Background/Objectives: Cervical cytology has for decades been the most widely used screening method for detecting cervical abnormalities. Within last decade, tests that detect HPV infections have become more prevalent. HPV-based screening, which is generally more sensitive, is currently being implemented in most Nordic countries. This transition evidently leads to changes in the performance characteristic of screening. Our aim was to compare screening test results in the Nordic countries by type of primary screening test using harmonized registry data. In addition, test result data will be published online on the NordScreen platform (nordscreen.org).

Methods: All test observations in the national screening registries in collaborating countries (Finland, Iceland, Norway, and Sweden) were collapsed into screening episodes. Subsequent tests within 90 days from the first test were combined into single episodes taking the most severe cytology and HPV test results into account. To ensure comparability between countries, only primary tests were included for further analysis. Positive test results were simplified into three categories: any positive, intermediate positive, and clearly positive. Intermediate positive indicates tests that usually warrant a repeat test whereas clearly positive results warrant a colposcopy. Harmonized screening data from each country were converted to standard format in each collaborative center, aggregated by the same R program script. Rate ratios for different test results were calculated using Poisson regression. Year, country, age group, and test method variables were used for adjusting and stratification.

Results: Primary HPV testing generally had higher test positivity rate compared to cytology, but the effect was dependent on age group and country. Time trends and differences between countries and age groups in test positivity rates will be presented.

Conclusions: Developing and comparing performance indicators with Nordic peers will help to highlight areas of suboptimal screening performance. Further research that incorporates histopathological data from colposcopies is crucial to more comprehensively assess the performance of screening. This will be performed in the next phase of the NordScreen project.

#0256

9 - HPV screening

PARTICIPATION IN HPV- AND CYTOLOGY-BASED CERVICAL CANCER SCREENING: RESULTS FROM A DANISH IMPLEMENTATION STUDY

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Background/Objectives: Cervical cancer screening by human papillomavirus (HPV) testing is more sensitive than cytology, and HPV-based screening is increasingly implemented. High participation is crucial for an effective screening program, but we have limited knowledge on whether shifting from cytology to HPV testing of clinician-taken samples affects participation. Our aim was to compare participation in HPV- and cytology-based screening in a large Danish implementation study.

Methods: In May 2017, HPV primary screening was implemented for women aged 30-59 years residing in four municipalities in the Region of Southern Denmark. We compared screening participation among women invited for HPV screening during the first year of implementation (HPV group, n=14,104) with participation among women invited for cytology screening in the same municipalities in the year before implementation (historical cytology group, n=11,931) and women invited for cytology screening in nine neighboring municipalities in the same year (contemporary cytology group; n=20,977). The invitation letter described the screening method (HPV/cytology), but otherwise invitation- and smear-taking procedures were identical in the three groups. All procedures were registered in the nationwide Pathology Databank. We calculated the cumulative probability of screening by time since invitation with the Kaplan-Meier method. Odds ratios (ORs) of participation within 6 months were estimated by logistic regression, adjusted for age, education, employment and country of origin based on information from Danish registers.

Results: When comparing the HPV group with the contemporary cytology group, the probability of screening participation was virtually identical at 6 months (58.4% [95% CI, 57.6-59.2] vs 58.8% [95% CI, 58.1-59.4]) and 1 year (69.9% [95% CI, 69.1-70.7] vs 70.0% [95% CI, 69.3-70.6]) after invitation. The odds of participation did not differ between the HPV and contemporary cytology groups (ORadjusted=0.97; 95% CI, 0.93-1.01). When comparing the HPV group with the historical cytology group, the probability of screening participation was slightly higher in the HPV group at 6 months (58.4% [95% CI, 57.6-59.2] vs 55.8% [54.9-56.7]) and 1 year (69.9% [95% CI, 69.1-70.7]) vs 68.1% [95% CI, 67.3-69.0]) after invitation. The odds of participation was slightly higher in the HPV group than in the historical cytology group (ORadjusted=1.10; 95% CI, 1.05-1.16).

Conclusions: Introduction of HPV-based screening did not result in lower screening participation compared with cytology-based screening. These results are reassuring for ongoing efforts to implement HPV-based primary cervical cancer screening.

#0422

9 - HPV screening

SHIFTING SANDS - HPV SCREENING IN THE POST-VACCINE ERA

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Background/Objectives: HPV vaccination is impacting screening populations. A recent meta-analysis confirms an age-dependent reduction of 66-83% in HPV16/18 prevalence with a corresponding decrease in CIN2+ of 31-51% (13-24 year olds) (1). This impact will be accelerated with the introduction of 9-valent coverage in catch-up women (< 45) [today] and primary vaccinated girls [2030 and beyond]. In populations with good coverage herd immunity is also reducing prevalence in non-vaccinated women.

Methods: We evaluate the impact HPV vaccination by reviewing recent literature and two BD OnclarityTM HPV Assay vaccine studies, one in the UK and the other nested within our US-PMA clinical trial.

Results: Global data consistently reports reduction in prevalence and disease associated with vaccine types. However, the published literature is divided on whether or not HPV type replacement (increased prevalence of non-vaccine target types) is occurring. BD Onclarity vaccine data from a UK and US age-matched controls suggests that there is indeed a significant increase in non-vaccine types in vaccinated women: In the UK catch-up vaccination (SHEVa) study of 1,000 age-matched controls, vaccinated women with low-grade cytology had a significantly higher proportion of non-vaccine types [$p < 0.0001$]. In the PMA trial cohort, vaccinated (n = 2,977) vs. unvaccinated (n = 11,176) women aged 21-34, also reported an increased prevalence of non-vaccine types [Odds Ratio = 1.2 ($p = 0.009$)]. Recent CDC data also confirms this finding, reporting an increase in non-vaccine types in vaccinated versus unvaccinated women (prevalence ratio as high as 1.7 in 25-29 year olds (95% CI = 1.49-1.95) (2). However, this does not necessarily imply increased virulence or disease caused by non-vaccine types and thus, the overall clinical significance remains unclear.

Conclusions: Vaccination is changing the prevalence of both target and non-target HPV types. Extended genotyping (beyond HPV 16/18) will be necessary to navigate this dynamic screening landscape. Extended genotyping can provide a more complete risk profile by: Accurately detecting both mixed and single infections with a clinically validated cut-point Identifying the next tier of post-vaccination high-risk types associated with CIN2+ disease Facilitating tracking of persistence, which is responsible for all cervical disease Providing population data on non-vaccine type prevalence to monitor for any changes in HPV type virulence HPV16/18 typing will remain important to monitor vaccine efficacy and for unvaccinated women but will become less relevant as a triage tool over time.

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#0375

14 - Screening methods

REDUCING FALSE POSITIVE REFERRALS IN HRHPV POSITIVE WOMEN WITHIN THE DUTCH CERVICAL CANCER SCREENING PROGRAMME: A MODELLING STUDY

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Background/Objectives: With the implementation of primary high-risk human papillomavirus (hrHPV) screening in the Netherlands, an increase was observed in the number of unnecessary referrals compared to the old cytology-based screening. Various triaging strategies have been proposed in the literature for triaging hrHPV positive women, including genotyping and triaging based on the severity of the cytological classification. Evaluating the optimal triage strategy for the Dutch setting is necessary prior to any change to the current programme.

Methods: The microsimulation model MISCAN was used to calculate the number of screening tests, referrals, cervical intraepithelial neoplasia (CIN)/cancer diagnoses, cancer deaths, life years and quality adjusted life years (QALYs) gained and costs for ten different triage strategies, each with either 6, 12 or 18 months until repeat testing. Costs and effects were discounted annually by 4% and 1.5% respectively. Univariate sensitivity analyses were performed adjusting participation rates and disutility assumptions. Further sensitivity analysis will be conducted on 3% discount rates and different cytology test characteristics.

Results: Extending the time to repeat testing from 6 to 12 months reduced unnecessary referrals (<=CIN 1) by 7%, with no impact on cervical cancer incidence, mortality or QALYs. In addition to 12 month time to repeat testing, increasing the cytology threshold for direct referral from ASC-US to LSIL and implementing hrHPV16/18 genotyping both resulted in further reductions in unnecessary referrals (LSIL referral: -32%; genotyping: -34%) and increased the positive predictive value for CIN2+ (LSIL referral: 26%; genotyping: 27%). Increasing the cytology referral threshold resulted in a small increase in incidence and mortality (2% and 3% respectively), whereas genotyping resulted in little to no increase in incidence and mortality (1% and -1% respectively). Consequently, increasing the cytology referral threshold and adding genotyping resulted in a loss of QALYs (7% and 4% respectively). Sensitivity analysis found that unnecessary referrals, incidence and mortality were relatively insensitive to the participation rate. Adjusting the disutility assumptions reduced the negative effects of both suggested strategies on QALYs.

Conclusions: Results indicate that extending time to repeat cytology testing from six to 12 months reduces the number of false positive referrals with little to no effect on incidence of, or mortality from, cervical cancer. Further reductions can be achieved by tightening the referral cytology classification from ASC-US to LSIL and by implementing genotyping.

#0687

9 - HPV screening

Predict and Prioritize: detection of CIN3 lesions up to 5 years before their development using a methylation classifier.

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Background/Objectives: Methylation markers have shown great potential for diagnosis of CIN2/3 lesions. This study aimed to continue further and assess the performance of a DNA methylation classifier, S5, at predicting progression of histologically normal but high-risk HPV positive samples to high-grade cervical lesions using baseline samples taken up to 5 years before diagnosis. A second aim was to confirm the usefulness of S5 to detect prevalent CIN2/3 lesions for triage of high-risk HPV women.

Methods: We used archived liquid-based cytology material from the prospective randomised ARTISTIC trial. The S5 classifier comprising target regions of host gene EPB41L3 and viral regions of HPV16, 18, 31 and 33 was assayed by pyrosequencing on 1187 samples (327 CIN2/3 samples and 860 controls).

Results: S5 could discriminate between the baseline sample of progressers to CIN2/3 (median=1.3) and women who did not progress (median=0.7) using samples that were, on average, taken 5 years before the high-grade disease was diagnosed. S5 performed better than HPV typing with HPV16, HPV16/18, HPV16/18/31 or HPV16/18/31/33 at detecting CIN2/3 or CIN3 only. The AUC of S5 for detecting CIN3 at round 1 was 0.85 (95%CI 0.80-0.90). For HPV16/18 genotyping, the AUC was 0.74 (95%CI 0.67-0.80). S5 was more sensitive but less specific than HPV typing. At the 0.8 cut-off for S5, sensitivities were 84% (95%CI 77-90%) for detecting CIN2/3 and 92% (95%CI 88-97%) for detecting CIN3, specificities were 56% for both CIN2/3 and CIN3 respectively. Using HPV16/18 typing to detect prevalent CIN2/3 and CIN3 gave a sensitivity of 56% (95%CI 48-65%) and 67% (95%CI 56-77) respectively and a specificity of 65% for both outcomes.

Conclusions: S5 classifier could be an accurate triage test for hrHPV women in cervical cancer-screening programmes. Its implementation would be cost-effective and avoid unnecessary referral to colposcopy of women clearing the infection. S5 could also be used to identify women at risk of developing CIN3 lesions within 5 years who could be followed closely.

FC 11 - Self-sampling (I)

#0234

10 - Self-sampling

INCREASED PARTICIPATION IN CERVICAL SCREENING AMONG LONG-TERM NON-ATTENDEES BY THE USE OF VAGINAL SELF-COLLECTED SAMPLES

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Background/Objectives: Cervical cancer is preventable through screening and in Sweden the nationwide cervical screening coverage is 83%. Women who do not attend to screening are at greater risk of cervical cancer. To increase participation among non-attending women, self-collected vaginal samples for detection of high-risk human papillomavirus (hr-HPV) is an option. The aims of this study were to investigate the response rate of a self-collected vaginal hr-HPV sample sent to long-term non-attendees and the prevalence of severe cervical dysplasia or cancer among the responders.

Methods: A vaginal hr-HPV self-sampling kit was sent to 19,766 women aged 30-70 years with no cervical screening sample for 7 years or more. The self-collected sample was analyzed by Aptima HPV mRNA assay (Hologic). Women positive for hr-HPV mRNA were invited for follow-up comprising a cervical sample for cytological analysis and renewed Aptima HPV mRNA testing.

Results: The response rate of the self-collected hr-HPV sample was 18.5% (3,649/19,766) and the prevalence of hr-HPV mRNA was 11.1% (401/3,608). Among hr-HPV positive women 85.5% (343/401) attended follow up, where 45.8% (157/343) had detectable hr-HPV in the cervical sample. At follow up the HPV mRNA test showed a positive predictive value (PPV) of 16.6% (26/157) for detection of cytological severe dysplasia. Histopathologically confirmed prevalence of severe dysplasia or cancer was detected in 0.85% ((31/3,649) 95%CI; 0.6-1.2%) among responders, including two cervical and one vaginal cancer. Several reminders had to be sent to some of the vaginally HPV positive women to get them to follow-up.

Conclusions: Self-collected vaginal hr-HPV samples increased participation in the cervical screening among long-term non-attendees by almost one fifth. Compared to regularly screened women the hr-HPV mRNA positivity rate was significant higher among long-term non-attendees in our study (11% vs. 7% in normal population, p-value<0.001), although the prevalence of histopathologically confirmed severe dysplasia or cervical cancer was not increased. The presence of hr-HPV mRNA among self-samples indicates suspicion of cervical disease. However, to identify individuals with cervical disease it is important that women with hr-HPV positive self-samples attend diagnostic follow up and repeated hr-HPV testing.

#0307

10 - Self-sampling

FEASIBILITY AND PRESUMED ADDED VALUE OF SELF-SAMPLING FOR HPV-BASED CERVICAL CANCER SCREENING USING A MIDWIFERY NETWORK ACROSS RURAL GREECE. THE GRECOSELF STUDY.

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Background/Objectives: Self-sampling for human papillomavirus (HPV) testing is an alternative to physician-sampling particularly for cervical cancer screening non-attenders [1-3]. GRECOSELF is a nationwide cross-sectional study utilizing a midwifery network and aiming to assess the added value of HPV-DNA testing in conjunction with self-sampling for cervical cancer screening, in relation to already existing opportunistic cytology-based screening (Pap testing).

Methods: Women, between 25-60 years old, who do or do not attend opportunistic cervical cancer screening and reside in rural areas of Greece were approached by midwives, of a nationwide midwifery network, and were given a self-collection kit (dry swab) for cervicovaginal sampling along with the necessary instructions. They were also asked to answer a questionnaire about their cervical cancer screening history. Each sample was tested for high-risk (hr) HPV with the cobas®HPV test, Roche®, which detects HPVs 16 and 18 separately, and HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 as a pooled result. HrHPV positive women were referred to colposcopy, and biopsy in case of abnormal colposcopic impression. If biopsy was normal the woman was referred to routine screening, if there was Cervical Intraepithelial Neoplasia (CIN) grade 1 or 2 or worse (CIN2+) she was referred to follow up or appropriate treatment respectively.

Results: Between May 2016 and November 2018, 13,111 women were recruited. Of these, 12,787 women gave valid answers in the study questionnaire and had valid hrHPV-DNA results; hrHPV prevalence was 8.3%; high-grade cervical/vaginal disease or cancer (HGD+) prevalence was 0.6%. Opportunistic, cytology-based screening, conducted on the study population before enrolment had detected 169 cases of presumed, based on self-reporting, HGD+, whereas hrHPV-DNA testing performed on this population within GRECOSELF led to the detection of 77 additional HGD+ cases; an increase of 45.6%, (36.6% when restricting the analysis to women tested within 3 years prior to enrolment). Among the 77 women detected with CIN2/3 or cancer, 59 had a Pap test during the last three years (abnormal in only 7 cases), 13 before the last three years, and 5 did not have a Pap test in the past. Of note, there were two cases with cervical cancer, in both of which Pap test was reported to be "negative".

Conclusions: HrHPV-DNA detection on self-collected cervicovaginal samples using a dry cotton swab, provided by visiting healthcare workers (midwives), is a method presumably adding significantly to opportunistic cytology-based screening.

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#0291

10 - Self-sampling

HIGH RISK HPV PREVALENCE AMONG URBAN ETHIOPIAN WOMEN USING VAGINAL SELF-SAMPLING

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Background/Objectives: In Ethiopia, cervical cancer is considered the most common malignancy amongst women(1). Ethiopia utilizes visual inspection with acetic acid (VIA) as the main preventative strategy. The introduction of HPV self-sampling has been shown to increase acceptance to cervical cancer screening and coverage in different settings(2). Objectives: To evaluate the participation rate for a free of charge self-sampling HPV test in an Ethiopian cohort and to assess the prevalence of HPV.

Methods: An open invitation for all women (N=5950) at Ethiopian Airlines in Addis Abeba between 18-70 years of age, with no prior history of cervical cancer or hysterectomy was offered. A vaginal self-sample (Aptima multitest swab, Hologic) was performed by the women after informed consent. After pre-heating samples at 90°C for 1h they were analyzed by Aptima HPV mRNA assay (Hologic). The HPV positive samples were further genotyped using MGP-PCR Luminex HPV DNA assay. HPV mRNA positive women were followed up at their own health clinic using liquid based cytology according to local protocol.

Results: In 3 days during October 2018,183 women performed a vaginal self-sample, a participation rate of 3,1% (183/5950). The HPV prevalence in this group was 21% (37/180). Among the 37 HPV-positive cases, 10 different high risk HPV types were detected with low prevalence (<2.2%) for each HPV type. The test results were given over phone; and 97% (36/37 HPV positive were reached. Among 69% (25/36) of the HPV positive women pap smears were collected within 6 months with one HSIL, one ASCUS and one LSIL detected.

Conclusions: In this Ethiopian urban cohort of women the participation rate for self-sampling was low probably due to the short screening duration. But in comparison to the 132 cervical cytology screening tests collected the last 3 years, participation in cervical cancer screening improved A fifth of the women demonstrated presence of vaginal HPV. The low proportion of women participating in follow-up after a positive HPV result stress the importance to improve the information and logistics to implement screening in communities with no prior effective screening program.

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#0044

10 - Self-sampling

Survey of the acceptance status of HPV self-sampling in cervical cancer screening population

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Background/Objectives: To investigate the acceptance of HPV self-sampling mode in cervical cancer screening population and explore its feasibility.

Methods: From March 5 to 15, 2018, researchers investigated women who participated in cervical cancer screening organized by Beijing Shunyi Women′s and Children′s Hospital in the form of questionnaires. Questionnaires were conducted on their acceptance status and the factors that affect the self-sampling experience. The specific contents of the questionnaires were as follows: (1) The experience of using self-sampling included operability, comfortable, sample time-consuming, bleeding or not after sampling; (2) Psychological changes after self-sampling, including the willingness to accept self-sampling again, the worrying problems during self-sampling process. According to whether or not have operating video guidance, the self-sampling experience and psychological changes after self-sampling were compared.

Results: (1) There were 1375 women participated in the questionnaire survey. 86.55% of them thought the self-sampling was convenient, 78.40% thought it was not uncomfortable, 88.58% thought the sampling time was fast (less than 5 minutes), 94.04% self-sampling without bleeding. 83.27% were willing to self-sampling for cervical cancer screening again, 85.82% were afraid of inaccurate sampling. (2) Among the 1375 women, 1202 were in the video guidance group and 173 were in the non-guidance group. The self-sampling experience of women in video guidance group was better than that of non-guidance group in operability, comfortable, sampling time-consuming and bleeding after sampling. The proportion of women who willing to self-sampling again was higher than that of non-guidance group (86.69% and 59.54%, respectively). The proportion of women who worried operating incorrectly was lower than that of non-guidance group (11.23% and 32.37%, respectively). The difference was significant ($P < 0.05$).

Conclusions: Self-sampling for HPV testing in cervical cancer screening is easy to operate and has little discomfort complaint. It is feasible in cervical cancer screening. Operational video guidance during the screening process can effectively improve the women's experience and willingness to self-sampling again in the future.

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#0089

10 - Self-sampling

Performance and acceptability of self-collected samples in HPV detection

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Background/Objectives: HPV DNA testing is more sensitive than cytology in detecting pre-cancerous cervical lesions. It can be performed using self-collected samples, increasing the adherence rate of national and local cervical screening, particularly when logistical and cultural barriers are in place. Several studies have been showed comparable accuracy between self-and clinician-collected samples, although variable target populations and assays were recruited. Aim of the present study was to assess the accuracy of HPV testing using self-collected vaginal and urine samples or specialist-collected samples.

Methods: Women, aged 25-64 years, referred to the LILT (Italian League Against Tumors) gynecological center of Sassari, Italy,were enrolled and, then, underwent a specialist-collected sampling. A commercial kit including devices to collect vaginal (FLOQSwabsTM, Copan) and urine (UriSwabTM, Copan) samples was provided together with a questionnaire aimed at evaluating the acceptability and adherence of self-sampling. Specimens were tested for 14 high-risk(HR) HPV genotypes using Anyplex II HPV HR detection kit (Seegene Inc, Seoul, Korea).Diagnostic agreement was assessed with the Cohen's K statistic.

Results: 196 women (mean age: 44.5 years) were recruited between December 2018 and May 2019;~20% did not participate previously to screening. HR-HPV genotypes were detected in 20% of the samples; the most prevalent were HPV-16, -31, -51, and -56. Agreement between positive and negative results for specialist- and self-collected vaginal samples, as well as between vaginal and urine self-collected specimens was highest (agreement: 0.959; K Cohen: 0.796 for both comparisons). Similar concordance was found between vaginal specialist-collected and urine self-collected samples (agreement: 0.939; K Cohen: 0.669). 85% reported a higher acceptability of the self-collection method in comparison with the conventional sampling, because of its simplicity and convenience.

Conclusions: Our preliminary results showed comparable high diagnostic accuracy of the HPV-DNA testing following self-and clinician-collected sampling. The acceptability and its potential cost-effectiveness need further assessment and confirmation for the inclusion into organized cervical screening program in the near future.

#0414

10 - Self-sampling

POSSIBLE IMPACT OF KNOWLEDGE ABOUT HPV AND SELF-COLLECTION IN MEN WITH UNVIABLE BIOLOGICAL SAMPLES ON HPV TYPING

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Background/Objectives: One of the great challenges for detecting HPV in men continues to be the collection of biological material. Studies that have been conducted in men, for HPV analysis, rely on epidermal debriding followed by specimen collection by a saline-moistened Dacron swab. The agreement regarding HPV genotyping between samples collected by health professionals or by self-collection can varied broadly and neither clinicians nor patients routinely obtained samples with consistently higher or lower prevalence at specific genital sites. The aim of this study is to evaluate how much the knowledge level about HPV can affect the self-collection procedure and viability of samples.

Methods: Data collection and sampling of this work are part of POP-Brazil study which is a multicentric study that enrolled young 16 to 25 years in primary care units in 27 cities at Brazil. All participants answered questions regarding HPV knowledge thought structured validated questionnaire with 14 questions. This score was divided in quantiles where the first quantile means low or no knowledge about HPV and the third represents a good knowledge. A genital sample was collected and analyzed by Linear Array HPV Genotyping Test (Roche Diagnostics). Biological sample screening was performed on the web data platform (SIS), where temperature and sample conditions were daily monitored. In all analyses a qui-square was used to evaluate the association between knowledge and valid samples. We used SAS software, version 9.4 with significance level of 5%.

Results: From the 2200 penile samples self-collected, 1037 (47%) were considered inadequate for HPV genotyping. We analyzed if the level of knowledge was associated with self-sample collection failure. Those with higher levels of knowledge about HPV presented a higher performance in self-collection sampling (26.42% vs 20.64% $p = 0.022$) comparing to lower knowledge level. It was also observed significant association between the educational level and participants knowledge related to HPV ($p < 0.0001$).

Conclusions: For reliable and consistent sample collection, it is essential that participants understand the procedures that need to be done. The fail to provide a valid HPV sample can be due to different causes as insufficient or degraded cellular material, poor extraction or the presence of PCR inhibitors or sample collection issues. Thus, accessing people's knowledge about HPV can be a proxy of health education and can impact in the viability of the samples.

FC 12 Public Health / Education (II)

#0167

38 - Public health

The Number and Gender of Children Synergistically Impact on Mothers' Practice of HPV Testing and Attitudes towards HPV Vaccination in Shenzhen, China

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Background/Objectives: In China, severe restrictions have been placed on the number of children that a mother could have for many years. Affected by the changed birth control policies in China, a large portion of mothers with only one child and subsequently an increasing number of mothers with two or more children exist. Parental or maternal factors may involve in children's health decision, for example, previous studies found that mothers' awareness of HPV and its vaccine was associated with HPV vaccine acceptability for their children, whereas studies seldom pay attention to detect the impact of children on mothers' knowledge and acceptability to HPV and its vaccine. It's reported that the number of children may impact on mothers' health concept and behavior, there is a need to understand the role of children in mothers' acceptability of HPV testing and vaccination.

Methods: A cross-sectional survey was conducted between January and June 2015 in Shenzhen, China, recruiting representative females from healthcare institutions through the Cervical Cancer Prevention Network. A self-administered questionnaire was used to collect information about socio-demographic characteristics, awareness and specific knowledge of HPV and its vaccine, the willingness to vaccinate themselves and their daughter(s) with HPV vaccine. Multivariate logistic regression was applied to explore possible associations and multiplicative interactions.

Results: A total of 9058 females were included. Women with one child had higher awareness of HPV (49.9% vs. 34.0%, P<0.001) and its vaccine (26.0% vs. 15.0%, P<0.001), and were more likely to receive HPV testing (38.1% vs. 25.8%, P<0.001) and vaccination (65.7% vs. 60.6%, P<0.001) than those with two or more children. Multiplicative interactions between the number of children and having daughter(s) on women's practice of HPV testing and willingness of HPV vaccination were detected (P valuesfor interaction were 0.014 and <0.001, respectively). Mothers having one child who was a daughter were more likely to receive HPV testing (OR: 1.534, 95%CI: 1.245-1.889) and HPV vaccination (OR: 1.630, 95%CI: 1.378-1.928) than those having two or more children but without daughter(s).

Conclusions: Our findings provide novel insight to cervical cancer prevention that a smaller number of children help to improve mothers' awareness of HPV and its vaccine, promote their practice for HPV testing, and acceptability to HPV vaccination. Having daughter(s) synergistically interact with fewer children to facilitate mothers' positive involvement against HPV infection.

References: Not involved.

#0243

38 - Public health

HOW TO ACHIEVE HPV-RELATED DISEASES CONTROL IN ITALY? RECCOMENDATIONS FROM A CONSENSUS CONFERENCE

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Background/Objectives: Albeit the public health relevance of vaccination against Human Papilloma Virus (HPV) and the 95% coverage goal set by the National Immunization Plan, vaccination coverage in 12-years old adolescents in Italy is still around 70%. Because of the importance of reaching coverage goal for the control of HPV-related diseases, this project aimed at developing recommendations on how strengthening HPV vaccination at national level.

Methods: The project had two objectives: the first one was to release recommendations toimprove vaccination coverage among adolescents and the second one was to define approaches to promote the vaccination in further targets. The project relied on both a systematic review of available literature and a two-step panel consultation which ended on a consensus conference. The systematic review followed PRISMA recommendations and collated together the evidence about strategies put in place worldwide to increase vaccination uptake. On the other hand, a questionnaire and a televoting system were used to perform the panel consultation that involved ten experts belonging to Gynecology, Public Health, General Practice, Pediatrics and Consumers. Recommendations were formulated taking into account panel's opinions on a set of criteria drawn from the Evidence to Decision framework, namely relevance of benefits, strength of the evidence, feasibility, equity, acceptability and costs.

Results: The systematic review put together the evidence from 57 papers and showed that analyzed interventions are mostly effective and may be classified in three main groups on the basis of tools used, namely reminds, educational interventions or multicomponent approaches. Nevertheless, according to the panel consultation, a strong recommendation was only formulated on the use of reminds tailored to vaccine recipients and of multicomponent interventions targeting healthcare professionals. As far as other potential targets of the vaccination are concerned, the panel released a strong recommendation on the promotion of vaccination among women treated for HPV-related diseases and fertile women not yet vaccinated, including 25 years old women. Furthermore, a strong recommendation was elaborated on catch-up initiatives, in particular in the eighteenth year of life.

Conclusions: This project allowed to develop the consensus on several strategies to strengthen HPV vaccination at national level considering both adolescents, who are already the primary target of the national campaign, and other targets. The implementation of these strategies could bring Italy to control HPV-related diseases.

#0373

38 - Public health

Women not HPV-vaccinated as children are less likely to be screened as adults

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Background/Objectives: The combination of organized cervical cancer screening and childhood HPV vaccination programs has potential to eliminate cervical cancer in the future. However, only women attending both programs gain full protection, whereas combined unvaccinated and unscreened women remain at higher risk of developing cervical cancer. Our objective was to analyze the association between non-attendance in free-of-charge HPV vaccination and non-attendance in free-of-charge organized cervical cancer screening adjusted for socio-economic factors.

Methods: A nationwide register-based cohort study including all women born in 1993. Consistent with women eligible for both HPV vaccination and first cervical cancer screening. Logistic regression models with corresponding 95% confidence intervals (CI) were used to estimate the odds ratio (OR) of non-attendance in cervical cancer screening among unvaccinated women compared to vaccinated women. Furthermore, to determine if the association between non-attendance in vaccination and non-attendance in screening was modified by native background, stratified logistic regression models were used along with the Wald test for interaction.

Results: A total of 24,828 women were included in the study. Among vaccinated women, 61.4% attended cervical cancer screening;whileonly 39.0% of unvaccinated women attended cervical cancer screening. Unvaccinated and unscreened women were more often non-native and had the lowest socio-economic status. The adjusted odd of non-attendance in screening was 2 times higher for unvaccinated women compared to vaccinated women (adj. OR 2.07[95% CI: 1.88-2.28]). Stratifying by native background, unvaccinated native women had the highest adjusted OR of non-attendance in screening compared to non-native women from both Western and non-Western countries (adjusted ORs of 2.2 [95% CI: 2.0-2.4], 1.3[95% CI: 0.6-2.8], and 1.5 [95% CI: 1.1-2.0], respectively) (Wald test p=0.019).

Conclusions: Among native women, non-attendance in HPV vaccination and non-attendance in screening seem to be signs of generally poor health-preventive behavior, whereas non-attendance in HPV vaccination and screening among non-natives from non-Western countries seem to be influenced by unrelated factors. Therefore, it is recommended to develop a differentiated and culturally sensitive approach in order to enhance cervical cancer prevention across different natives.

#0478

38 - Public health

Socioeconomic differences in cervical testing within and outside the screening program

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Background/Objectives: The Finnish cervical cancer screening program has proven to be effective. However, Pap-testing outside the organized program has been common, and these tests are not centrally registered. It is not fully known whether certain socioeconomic or ethnic groups have tests outside the program more often than others. This can now be studied for the first time using a nationwide, individual-level research dataset including Pap and HPV -tests within and outside of the program, socioeconomic status and mother tongue. The aim of this study was to examine socioeconomic and ethnic differences in the coverage of cervical testing within and outside the organized screening program in Finland.

Methods: We had a cohort of 1,2 million women aged 30-60, residing in Finland in 2014. Data on Pap and/or HPV -tests within and outside the screening program were collected from the Mass Screening Registry, the pathology laboratories and the health insurance reimbursement registers. Information on the cohort's socioeconomic status and mother tongue was collected from Statistics Finland. Five-year population coverages (2010-2014) of tests within the screening program and outside it were assessed across the different groups.

Results: Of the study cohort, 86% were tested at least once during the five years either in the organized program or outside it. Appr. 37% attended only at the organized screening, 18% only for external testing and 31% attended at both. Coverage of tests outside the program was the highest among native speakers, students and women of the highest socioeconomic classes. The proportion of women with no tests, whether within the program or outside it, was the largest among pensioners, unemployed and non-native speakers.

Conclusions: There are differences between socioeconomic and ethnic groups in the coverage of Pap and HPV -testing. Tests outside the program seem to concentrate on women with presumably good access to health services or on young students who are at a low risk of invasive cervical cancer. Improving both health equity and cost-effectiveness calls for interventions, more research and follow-up.

#0507

38 - Public health

PERCEPTIONS ON REASONS FOR PAP AND HPV TESTING AMONG HEALTHCARE PROVIDERS IN FINLAND

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Background/Objectives: In Finland an extensive opportunistic screening practice that concentrates especially on younger women exists alongside the national screening program. Awareness of the attitudes and perceptions on cervical cancer screening by healthcare providers is essential for assessing procedures to improve the current screening practice. Aim of the study is to assess healthcare providers' perceptions on indications for Pap- and HPV-testing. The eventual aim is to reduce unnecessary screening and enhance adherence to cervical cancer screening guidelines.

Methods: An anonymous electronic survey was conducted during spring 2018 among approximately 3000 healthcare providers in five bigger cities in Finland. Healthcare providers' attitudes, beliefs, knowledge and practices on cervical cancer screening related topics were asked were asked. The target group were doctors, nurses, midwifes and laboratory personnel in the public primary, student and private healthcare and gynecology units in the secondary and tertiary healthcare.

Results: 531 health care professionals attended the survey. Detecting cervical cancer precursors or cervical cancer were identified as reasons for a screening pap test by majority. Respectively, a gynecological bleeding disorder or a follow-up after a previously detected cervical cancer precursor as reasons for a diagnostic pap test. However, there also seems to be confusion regarding the concept and indications for a pap test and 47 % of the respondents considered that the first pap test in a screening purpose should be taken a few years after the first sexual intercourse. 70 % considered HPV-test should be used as a screening test, 27.8 % of them regarding HPV-test applicable for screening women aged under 30 years.

Conclusions: There are discrepancies in the perceptions of health care professionals with information available on natural history, evidence of benefits and harms, and current clinical guidelines on cervical screening services. Our study will likely give important information to determine procedures to intervene in the current screening practice.

#0097

36 - Health education

DEVELOPMENT AND VALIDATION OF A PEER EDUCATION PROGRAM FOR CERVICAL CANCER PREVENTION

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Background/Objectives: Due to low rates of cervical cancer (CC) screening and HPV vaccination, the incidence of CC among young women in Japan is increasing1).To change this situation, effective health education for young people is critical. In this study, we aimed to validate the benefits of peer education (PE) among students of a college for health educators.

Methods: This study was conducted in Japan Women's College of Physical Education (JWCPE) after approval by the institutional ethical committee. In 2016, a baseline survey was conducted with students of all grades (n=1904), including age, knowledge about risk factors for certain cancers, and the Japanese version of the European Health Literacy Survey Questionnaire to assess health literacy (HLS-EU-Q47). Eight 3rd year students who volunteered to be peer educators were provided with lectures and basic education materials about CC prevention by health professionals. Afterward, the peer-educators created their own education materials and gave 30 minute PE lectures to 2nd year students (n=500). In 2017 and 2018, the same survey as the previous year was administered to students who were involved in the PE program (n=1939). Remarks from student evaluations were grouped into eight subcategories across three domains. The effectiveness of the PE was tested using differences-in-differences regression, comparing changes in questionnaire domain scores between the 3nd year students of 2017 and 2018.

Results: The over-all HLS-EU-Q47 scores among 2016 students in all three domains (HC: Health care, DP: Disease prevention, HP; Health promotion) were higher in the follow-up surveys in 2017 and 2018. Notably, the peer educators showed robust increases in the DP domain score ($p<0.083$) and overall HL score ($p<0.033$).

Conclusions: Our findings showed significant effects of PE to the peer educators rather than to the students who received PE lectures, suggesting the usefulness of proactive PE activities to improve health literacy among young women. In addition to the improvement of knowledge, we further studied behavioral changes toward CC prevention among the women who participated in the PE program.

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#0541

36 - Health education

USE OF A GAME-BASED LEARNING TOOL TO INFORM THE PUBLIC ABOUT HPV AND NUDGE WOMEN TO ATTEND CERVICAL CANCER SCREENING

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Background/Objectives: Lack of knowledge about HPV and the available prevention methods is an important barrier to reducing the burden of HPV related diseases. New technologies can provide opportunities to increase awareness and influence health behaviour. A game-based learning tool, FightHPV, was developed with the aim of evaluating the effect of using a mobile app to improve screening participation.

Methods: Acceptability of the game was assessed via focus group discussions and a questionnaire. The app development has been described previously (1). Since its release on both Google Play and App Store in 2017, the app has been promoted in Norway via various media channels including Facebook. In the Norwegian version of the app, players had the opportunity to participate in a questionnaire study about their experience using the app, and in a registry-based study assessing the effect of the app on cervical cancer screening attendance. Screening data has been extracted for eligible women who have consented to the study and preliminary analyses are presented here.

Results: Of 86 study participants who completed the questionnaire in the app, 60 (69.8%) reported having learned quite a lot or very much about HPV from playing the game, and 53 (61.6%) reported having learned quite a lot or very much about cervical cancer screening. Of 593 eligible women who consented to the registry-based study, 82 (13.8%) had not attended for screening by cytology or HPV test in the 3.5 years prior to entering the study, including 39 (6.6%) women who had never before attended cervical cancer screening. Among these 82 underscreened women, 65 (79.3%) attended for screening by cytology or HPV test following inclusion in the study, including 22 of the women who had never previously attended screening.

Conclusions: Women who downloaded FightHPV and consented to participate in our study had screening participation rates above that of the Norwegian population as a whole, suggesting that health promotion interventions may be more appealing to those who are already health conscious. Nonetheless, we did manage to recruit women who had not attended the last screening round, including women who had never attended screening before, and almost 80% of those women went on to take a screening test after joining the study. The next step in our analysis will be to match these women with controls who did not play the game to assess if the game can be said to have influenced participation in screening. These further analyses will be controlled for socio-economic status.

References: 1. Ruiz-López T et al. FightHPV: Design and Evaluation of a Mobile Game to Raise Awareness About Human Papillomavirus and Nudge People to Take Action Against Cervical Cancer. JMIR Serious Games 2019;7(2):e8540. URL: https://games.jmir.org/2019/2/e8540/ doi: 10.2196/games.8540 PMID: 30958271

#0418

35 - Advocacy, acceptability and psychology

A GERMAN ONLINE SURVEY OF PATIENTS WITH CIN, HIGHLIGHTING THE PSYCHOLOGICAL DISTRESS DURING REPETITIVE DIAGNOSTICS CYCLES

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Background/Objectives: In the course of female cervical cancer screening, the lesions are detected by Papanicolaou tests (Pap smear) or HPV testing. These tests are well established, easy to perform and sensitive in detecting cervical neoplasia. Both tests are, however, not able to distinguish between those lesions which will convert into cancer and those which will heal spontaneously. Though the majority of lesions will show spontaneous remission over time, all patients with abnormal Pap or HPV test results will have to undergo follow-up testing and / or additional examination such as further cytology or HPV-testing, colposcopy, and biopsies of the affected region. This sequence of follow-ups creates a burden to women as they will have to stand the ongoing uncertainty whether cancer is already in progress or not. We designed a survey to address the question of psychological burden due to abnormal Pap smear results and/or positive HPV tests.

Methods: The online-survey had a semi-structured design, combining explorative questions with validated elements and participants went through a 37-item survey including the IES-R („Impact of Event Scale-Revised"- German Version) as well as parts of the CDDQ (Cervical Dysplasia Distress) questionnaires. Participants for the survey were recruited using online marketing (via Facebook and Google) and the community from "Myriam von M" on Facebook (posts with link to survey).

Results: We received 3753 questionnaires within 9 weeks. Participants had a mean age of 31.8 years and 35.3% are still in family planning. Almost half (46.6%) of the women indicated that they had 3 to 5 (32.1%) and more (14.5%) suspicious Pap smears. More than half of the women (53.1%) had already been affected for more than one year and more than 2 out of 3 women (69.3%) stated to be afraid of developing or being diagnosed with cervical cancer, whereas 49.4% expressed the fact they were even anxious about dying. More than two third of the participating women reported that their worries about the Pap (69.9%) and HPV (76.4%) findings are at least "quite a bit" (Scores 3,4 & 5 on a 5-point scale) and half (48.1%) stated that the risk of conizations as well as the risk of preterm birth is important to them and "clearly" to "severely" impacting their life (Scores 4 & 5).

Conclusions: This survey is the first of its kind to investigate the psychological distress during repetitive diagnostics cycles from patients with abnormal Pap / HPV findings and highlights important findings in relation to the unmet clinical needs of the participants. Better awareness of the psychological burden of disease and of available diagnostic or treatment options are needed which may help to improve patients quality of life.

#0355

38 - Public health

A GEOSTATISTICAL ALGORITHM TO BETTER IDENTIFY CONTEXTUAL AND CLINICAL FACTORS ASSOCIATED TO HPV VACCINE COVERAGE IN FRANCE

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Background/Objectives: Large disparities of the Human Papillomavirus (HPV) vaccine coverage rates (VCR) are observed over the French territory. The study aims at identifying clinical and contextual factors explaining such variations using geostatistical algorithms which will be adapted to HPV vaccination in France. Understanding which community-level or individual-level factors are associated with HPV vaccination is a key aspect for designing targeted programs toward VCR improvement.

Methods: At the community level, the HPV VCR were crossed over the French territory with a large number of data gathered in sociological, economic, clinical, political and behavioral categories for the year 2016. It includes agglomerated and geolocalized web and social network data. The analysis was driven in a spatially varying way in order to determine geographical areas which are homogeneous in regard to the observed correlations. In each geographical area, a factor analysis was performed to reduce redundant information.

Results: The study shows that HPV VCR spatial variations in France cannot be fully explained by a unique model. Rural areas were more influenced by political and sociological factors (especially socio-professional categories and education level), while urban areas were preferentially associated with economic and migration related factors. Two secondary geographical areas were determined: Ile-de-France and 10 North Eastern departments. Discriminating them was contributing to a better characterization of the VCR variations. The Ile-de-France was showing even more economic factors impact than the urban area as a whole, and the North Eastern departments located in the urban area were showing very high level of VCR despite a poor economic situation.

Conclusions: Our geostatistical modeling approach leads to a better comprehension of the HPV VCR disparities. That is the first time that such innovative method is applied to identify factors influencing HPV VCR. Using this model, future localized vaccination programs should be targeted in specific sub-populations of interest.

#0251

14 - Screening methods

DISTINGUISHING PRIMARY AND SECONDARY HPV SCREENING IN REGISTRY DATA

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Background/Objectives: Primary HPV-based screening for cervical cancer in Sweden was mandated in 2015, but in some regions older policies using secondary HPV-testing may still be in use. The capital region (Stockholm) introduced primary HPV screening as a randomized health care policy already in 2012. Because of the concomitant use of primary and secondary HPV-testing in Sweden it is difficult to analyze the data and assess quality indicators as different policies may have been used at the same time. As all labs register incoming samples in different series, we investigated if it was possible to use the laboratory series to assess if samples had been taken for primary or secondary HPV-testing.

Methods: All HPV-tests in Sweden between 2012 and 2018 were linked on an individual level to the data on cytologies. Data was analyzed per sample year, per laboratory and per registered sample series at the laboratory. Threshold values were derived based on assumptions of appropriate policy and used to discriminate the sample series into four groups; (a) primary HPV screening: i. HPV-negative samples should not have a corresponding cytology (P1>88%), ii. HPV-positive samples should have a corresponding cytology (P2>95%), (b) secondary HPV-testing (triage of primary cytology): i. all HPV-tests should have a corresponding cytology (S>95%), ii. only LSIL, ASCUS, ASC-H and AGC cytologies should lead to HPV-testing (L>35%), (c) HPV-testing of self-sampling: i. no corresponding cytology should exist (on the same sample, SS>95%), ii. HPV-positivity should not exceed 15% (POS<15%), (d) other/ unknown indication for HPV-testing: none of above criteria match.

Results: Between 2012 and 2018 there were 919 998 HPV-tests performed in Sweden, of which a majority was classified HPV primary screening (52%). Comparisons with data provided by the labs found that all sample series used for HPV primary screening were identified correctly. Other/ unknown indication was rather common (34%). Secondary HPV testing (9%) and self-sampling (5%) were not common. Compared to the data provided by the labs, on how they registered samples, the misclassification rate was only 3.4%. For 24% of the samples it was not possible to obtain any unambigous information from the laboratories on how the sample series had been used.

Conclusions: Using very basic assumptions and a simple classification algorithm based on threshold values it was possible to correctly classify 72% of all HPV data in Sweden without using any lab-provided data on indication of HPV testing. The classification is easily performed, requires little computational and administrative effort and is applicable to new HPV-data without prior knowledge of the polices in use.

Classification of HPV data

#0405

24 - Cervical neoplasia

EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HPV INFECTED WOMEN: CERVICAL REEPITHELIZATION, PERCEIVED STRESS AND TOLERABILITY EVALUATION

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Background/Objectives: In previous clinical studies a non-hormonal Coriolus versicolor-based vaginal gel (CVVG) has shown to significantly influence the re-epithelization of the cervix and the rebalancing of the vaginal microbiota that favors the natural process of vaginal immunity. The objective was to evaluate the tolerability and the effect of the CVVG on the cervical re-epithelialization and the perceived stress in patients with HPV-dependent atypia (ASCUS and LSIL) and associated colposcopic alterations.

Methods: Multicenter, randomized, open-label, parallel-group, usual practice controlled clinical trial (Paloma Clinical Trial). Unvaccinated HPV+ women aged between 30 and 65 (mean age of 41 yo, evenly distributed among groups) with cytology of ASCUS or LSIL and concordant colposcopy image were included.Patients were randomized into 3 groups: A) CVVG 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months; B) CVVG 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months; C) Control group: no treatment (usual clinical practice). Changes in epithelialization of the cervix evaluated by standard colposcopy (and rated by investigators with a likert scale from 0= severe ectopy + bleeding to 5= normal) and in perceived stress evaluated by PSS14 were assessed at 6 months as secondary endpoints. Satisfaction and tolerability of gel were also evaluated. CVVG arms (A+B) were combined as treatment group and chi-square or Fisher test were used as appropriate.

Results: A total of 84 patients were evaluated (53 vs 31 in treatment and control groups, respectively). At 6 months, a statistically significant difference in cervix re-epithelization likert scale was observed: 4,51 vs 4.10 in CVVG and control group, respectively, p=0.017. A trend vs baseline was also observed in both groups: a stress reduction in CVVG group (21.13 vs 18.98) vs a stress increase in control group (17.72 vs 20.68). 58% of CVVG patients improved the PSS14 score vs 39% in control group. 87% of patients reported some degree of satisfaction with CVVG and none was unsatisfied. 11 out of 64 CVVG patients included in the safety sample reported 22 adverse events (AA): 7AA were possible/probable related to treatment (burning/stinging/itching), of which all were classified as mild/moderate and only in 2 cases caused permanent treatment withdrawal.

Conclusions: After the six-month treatment period,CVVG has shown a statistically significant difference in cervix re-epithelization and a positive trend in perceived stress reduction. CVVG has shown a high satisfaction level and a good tolerability. Data of further studies should confirm these exciting results.

#0250

36 - Health education

HEALTH SAVING TECHNOLOGIES IN XXI CENTURY - BASIC CONCEPTS OF HPV-ASSOCIATED DISEASES CONTROL IN RUSSIAN FEDERATION.

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Background/Objectives: More than 17,587 women a year in Russian Federation are diagnosed with cervical cancer and about 40% of this women die. Therefore development and implementation of vaccination and screening programs of HPV associated diseases in Russian Federation is crucial.

Methods: Social survey was conducted among 2500 medical doctors and 13870 women of different Russian regions with regards to screening and vaccination of HPV-associated diseases. We developed professional competencies' models in educational programs both for medical personnel and for Russian Federation women population in general in order to evaluate efficiency of such programs.

Results: Professional competencies' model in educational programs for the medical personnel included visualizing, modelling media virtualizing, information management and CASE-system of decision making during continuous medical education technological process. Professional competencies' model in educational programs for Russian Federation women population in general included innovative technologies of interactive discussion of HPV-associated diseases.

Conclusions: Professional competencies' model in educational programs for the medical personnel helped to create and increase competency with regards to screening and vaccination of HPV-associated diseases by 12,5 times. Professional competencies' model in educational programs for Russian Federation women population in general enabled to perform planned vaccination at a level of 90-93% in different Russian Regions.

References: Kononova I.N., Bashmakova N.V., Dankova I.V. Vinokurova E.A. Professional competencies' model in educational programs for the medical personnel during organization of cervical cancer screening. - Russian Journal of Obstetrician and Gynaecologist 2019;19(2): 21-26

FC 13 - HPV testing and genotyping (II)

#0171

8 - HPV testing

WHEN, WHY AND HOW TO TEST HETEROSEXUAL MEN FOR HPV?

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Background/Objectives: Less has been discussed about heterosexual men's genital HPV detection for the past years. The reason might be, that the HPV associated penile cancer had been found very rare. We have learnt from the epidemiological studies that high percent of men carry this cancer causing virus. During sexual intercourse men can involuntary infect women which by time might lead to severe CIN or cervical cancer. Until the HPV vaccination reaches the expected coverage in the population this must be an issue. Using the sampling method suggested in previous publication, 52% of our male patients with HPV risk turned negative.

Methods: In our HPV Center a 3 day preparation period was recommended for patients before visits. Vigorous but painless technique was applied. The glans, meatus, coronal sulcus, foreskin, shaft, base of the penis, scrotums had been targeted. In case of healed condyloma the affected surface also was included (like mons pubis, anus). We finally determined the minimum quantity of scraped squamous cells needed for valid HPV testing.

Results: More than 90% of our male patients at HPV risk turned positive. Men having partners with HSIL or worse in monogam relationship were mostly negative. It reflects that HPV is not infectious any more if its DNA has been incorparated into the host cell and begun malignant transformation. HPV concordance appeared in couples within 6 months if one was HPV negative at the beginning of their sexual relationship and the condom use was infrequent. Interestingly „HPV exchange" occured mostly only after 4-5 years in couples carrying different HPV types at start. We have also found that consequent condom use protects 100% from the penis-cervix ping-pong effect in partners practising only vaginal sex.

Conclusions: Heterosexual men is advised to be tested and followed up when having1. female partner tested HPV positive, 2. hectic sexual life, 3. condyloma. HPV infected women w/wo cervical dysplasia could not eliminate the virus quickly and could not be cured entirely without knowing their male partners' genital HPV status. Men having more than 1 partner in the last 5 years should also be aware of their genital HPV status, because they might be risk for women. Use of our new genital HPV sampling method for men may have a scientific and clinical benefit in the future.

#0264

11 - Genotyping

EXTENSIVE HPV GENOTYPING REVEALS MULTIPLE INFECTIONS IN RELATION TO CERVICAL LESIONS

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Background/Objectives: HPV testing is enrolled in screening cervical cancer and precancerous lesions in various strategies. The relations between the virus and lesions have been extensively elucidated, but the multiple genotype infection is less investigated due to the limitation of methodology. In the current study, with a method of genotyping 21 HPV in a large quantity of cases, we aimed to further evaluate their relations.

Methods: Totally 73,596 patients with 21-genotyping HPV testing were retrieved from the database of the Department of Pathology, Obstetrics and Gynecology Hospital of Fudan University from January 2018 to April 2019, including 64,534 with pap co-test results, and 17,394 had histological diagnosis within 6 months after HPV testing. The HPV testing was performed by BMRT real time PCR assay (Jiangsu BioPerfectus Technology, Taizhou, China), which genotypes 13 hrHPV, 5 potential hrHPV and 3 low-risk HPV separately, as well as the titers estimated by comparing to the amount of human TOP3A DNA.

Results: Of the 16,230 (positive rate of 22.1%) hrHPV positive cases, 4,005 (24.7%) have multiple infection of as many as 9 types of hrHPV. When considering all 21 types, multiple infection rate is 29.3% (5,390/18,405). Of the 14 hrHPV involving HSIL+ cases, HPV53, -66, -59 were the 3 most likely to be enrolled in multiple infection, and HPV16, -18, -58 were the 3 least (Figure 1). Comparing single or multiple infection pattern of individual types, single infection of HPV 16 was more likely to develop HSIL+ than multiple pattern ($P<0.001$), indicating intermingled with other genotypes would alleviate the lethality of it. HPV 52, 35, 51 showed reversal pattern, indicating they were less likely to be pathogens individually. All other types showed no significant differences, indicating the capability of causing diseases independent (Table 1). The loading proportion of HPV16, no matter what quantity itself, were positively correlates with HSIL+ lesions (Table 2).

Conclusions: Extensive genotyping could identify some more lethal genotypes, such as 16, 58, and 52. HPV26, a potential hrHPV, showed a higher prevalence in HSIL+ lesions than some traditional hrHPV. The percentage of HPV16, other than the titer itself, showed correlation with the severity of squamous lesions, supporting the value of extensive genotyping and quantitation of viral titer.

#0456

11 - Genotyping

Follow-up results from the EVAH study: hrHPV genotyping as a marker of progression to ≥HSIL/CIN2 in a well described cohort

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Background/Objectives: Selection of women at risk for current and future ≥CIN2/HSIL is important for good treatment and follow-up in cervical cancer screening. Here, we present the 2-year follow-up results of women with histological ≤LSIL/CIN1 after an abnormal cytological screening result. We aimed to identify women at increased risk for histological progression to ≥CIN2/HSIL using hrHPV genotyping results of consecutively collected physician-taken smears.

Methods: 1115 women with an abnormal Pap-smear result were included in Barcelona, Spain. Women were followed-up with a physician-taken cervical sample and colposcopy with biopsy taking every six months for 2 years. Follow-up results from women who had a negative/CIN1 biopsy at the first visit to the colposcopy clinic and who were not treated by LEEP/hysterectomy after, were used to determine histological progression to ≥HSIL/CIN2. The main determinants studied were hrHPV genotype and persistence, clearance and shift of genotype-specific hrHPV infection. In addition, differences between women with infection with multiple genotypes, including multiple hrHPV infections, and combinations with or without HPV16 were studied.

Results: We found a significantly higher proportion of women with a multiple infection of HPV16 with other hrHPV genotypes with histological progression to ≥HSIL/CIN2 compared to women who did not progress by using genotyping results at entry. In sequentially collected samples, detection of a genotype specific persistent infection with HPV16, HPV31 or HPV39 gave a higher risk of histological progression.

Conclusions: Our results show that a hrHPV test without genotyping or with only partial hrHPV genotyping misses important information. Persistent hrHPV positive status, even if HPV16 has previously been demonstrated, cannot be assumed to be a persisting infection with the same genotype. In women with ≤LSIL/CIN1, detection of multiple infections and of genotype specific persistent infection could help detect women at risk of progression to ≥HSIL/CIN2.

#0484

11 - Genotyping

HIGH-RISK HPV NEGATIVE CERVICAL INTRAEPITHELIAL NEOPLASIA 2+: A RETROSPECTIVE ANALYSIS.

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Background/Objectives: Persistent High-Risk (HR) Human Papillomavirus (HPV) infection has been identified as the main risk factor for the development of cervical intraepithelial neoplasia (CIN) and invasive cervical carcinoma (ICC). In recent years, primary HR-HPV screening every 5 years has been widely recognized as the best strategy to detect and treat precancer before cancer develops, since it is more sensitive than cytology. However, reports of rare HPV negative cancers are motivating continued use of both HPV testing and cytology ("cotesting"). The aim of this study was to investigate the proportion of HR-HPV negative CIN and ICC and to analyse the distribution of Low-Risk (LR) genotypes in this subset.

Methods: Women undergoing conservative surgical treatment of CIN and ICC at the European Institute of Oncology, Milan, from January 2016 to December 2017, were retrieved from our archives and selected for a retrospective analysis. HR-HPV DNA assays with or without genotyping were performed on liquid-based cervical (LBC) samples before surgery. In case of negative HR-HPV test, the Roche Diagnostics Linear Array test was employed to detect LR genotypes on a post aliquot from LBC specimens, when available. The laboratory and histopathologic characteristics were tabulated by counts and percentages.

Results: Four hundred thirty-one patients were enrolled, with a mean age of 40.3 ± 9.4 years (range: 23-78) at the time of diagnosis. HR-HPV test results were available in 427 women, which were included in final analysis. The most prevalent histology was CIN3 (49.2%). Overall, 46 (10.8%) of patients tested HR-HPV negative. Among 360 CIN2+, 8.9% (32) were HR-HPV negative and Linear Array result was available only in 17 cases. HPV 73 was the most prevalent genotype (6 out of 17), followed by HPV 53 (4) and HPV 84 (3). Interestingly, HPV 26 was detected in one case of squamous ICC in both LBC and formalin fixed paraffin embedded cervical specimens. All women affected by HR-HPV negative CIN2+ except one were referred to colposcopy before surgery, because of abnormal pap smear findings (≥ LSIL).

Conclusions: Some HPV genotypes, including 73, 53 and 26, which are not currently included in approved HPV DNA tests, are extremely rare in CIN2+, as well other genotypes that have been historically classified as HR. However, they might be considered as possibly HR. Our results showed a not negligible proportion of HR-HPV negative CIN2+, suggesting that performing "cotesting" would not miss these cases, despite increased costs. Additional studies on HPV genotypes driving HPV negative CIN2+ are warranted to implement primary HPV testing in cervical cancer screening.

#0340

20 - New technologies

Development of a Novel, Simple, Quantitative and Comprehensive low-cost HPV and Sexually Transmitted Infections Assay using Next-Generation Sequencing

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Background/Objectives: Sexually transmitted infections (STIs) impose a major global health and economic burden for the patients, populations and healthcare. According to World Health Organization (WHO) there are over 376 million new STI infection cases per year. STIs can have serious impact on individual's health. Delayed diagnosis and inadequate treatment of STIs can result in complications with serious consequences such as infertility and cervical cancer. There is an urgent need for a comprehensive assay to detect multiple STIs simultaneously. Here we show a new assay that detects 27 HPVs and 13 STIs in one single reaction with a simple workflow using next-generation sequencing(NGS) technology.

Methods: Type/species-specific primers were designed for clinically relevant 27 HPVs and 13 STIs and two internal human gene controls which are used to estimate copy number per cell and to monitor cross-contamination, respectively. Amplification and barcoding of each sample is performed in a single-well PCR reaction and all the amplicons are pooled together and sequenced by NGS.

Results: Our results show that the new assay can detect all intended types/species with high sensitivity, specificity and uniformity. The entire workflow consists of four steps of DNA extraction, single-well and one-step amplification, sample pooling/library preparation and sequencing. The assay can be completed within 24 hours including 17 hours sequencing. Using this comprehensive assay, our results show that many samples are found to have more than one clinically important type/species present that go undetected.

Conclusions: We have developed a highly multiplex and comprehensive STI assay that uses low amount of DNA, detects and quantifies 27 HPVs and 13 STIs in one single-tube and one-step amplification reaction. Due to its simple procedure, the comprehensive STI assay is very low-cost and can be easily automated for different sample scales. The comprehensive STI assay can be used for screening, detection, research and epidemiological settings.

#0463

9 - HPV screening

RETROSPECTIVE ANALYSIS OF HPV GENOTYPING DATA IN CERVICAL CANCER SCREENING IN GERMANY

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Background/Objectives: Since the introduction of a cervical cancer screening program in Germany in 1971, incidence and mortality rates decreased by more than 74% [1]. Jan 1st, 2020, an organized cervical cancer screening program will be introduced [2]. Women between age 20 and 34 will participate in the annual cytological screening and women at the age 35 will receive a co-test (Pap smear/HPV test) with a three-years-interval. There will be no upper age limit. Does the prevalent HPV genotype offer improved risk stratification benefits for the development of cervical intraepithelial lesions (CIN)?

Methods: The retrospective multicenter study analyzed health data collected in three medical care centers. The BD OnclarityTM test (BD Diagnostics, Sparks, MD) was used for HPV testing. It is a real-time PCR assay that detects 14 HR-HPV genotypes (HPV-16, -18, -31, -45, -51 and -52, HPV-33/58 (P1), HPV-56/59/66 (P2), and HPV-35/39/68 (P3)) [3]. Three HPV subgroups were established for the risk assessment: HPV-16, -18, and -45 versus HPV-31, -51, -52, and -33/58 (P1) versus HPV-56/59/66 (P2) and HPV-35/39/68 (P3). The results were divided into three age groups (> 18 - <35, > 35 - <65, 65+). Munich Nomenclature (MN) III was used to evaluate Pap smears. Histologically confirmed CIN 2+- or CIN 3+-lesions served as surrogate endpoints.

Results: Overall, HPV-16 (20.6%) showed the highest prevalence followed by HPV-31 (11.1%) and HPV-51 (10.2%). For the three HPV subgroups, different odds ratios (OR) were observed concerning the agreed surrogate endpoints. A small number of confirmed CIN 2+ and CIN 3+-lesions were negative (at least for the tested HPV genotypes).

Conclusions: HPV genotyping could provide additional risk stratification benefits.

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#0309

8 - HPV testing

L1 AND E6/E7 BASED ASSAYS DETECT SIMILAR LEVELS OF HPV IN HIGH GRADE AND INVASIVE LESIONS OF THE CERVIX, OROPHARYNX AND PENIS

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Background/Objectives: Human papillomavirus (HPV) genotyping is a useful tool for epidemiological studies and increased evidence suggests it will also be beneficial for cervical screening management. Many of the HPV genotyping tests on the market target the detection of the late gene L1. However, there is an argument that late genes are more likely to be lost during disease progression via integration compared to certain early genes, particularly E6 and E7. The extension of this logic is that HPV tests that target E6/E7 are less likely to miss high grade disease - particularly cancer. However, the evidence base for this assertion is not well established.

Methods: A head to head comparison between L1- and E6/E7-based HPV DNA target amplification tests for the detection of HPV in high-grade and invasive disease within different biological matrices and anatomical sites was conducted. A panel of 298 samples was obtained from the Scottish HPV Archive. The panel consisted of FFPE biopsy of cancers of 1) cervix, n=50; 2) oropharynx, n=50; 3) penis, n=50; as well as biopsies from CIN3 lesions, n=50. Additionally, liquid-based cytology (LBC) samples from CIN3+ cases (n=98, from which 60 were cancers) were included in the study. All samples were tested with two L1-based assays [Optiplex HPV genotyping Assay (Diamex, Germany) and RealTime HR-HPV Assay (Abbott Molecular, USA)] and two E6/E7-based [EUROArray HPV test (Euroimmun, Germany) and Xpert HPV (Cepheid, USA)]. Primary outcome was to assess HPV positivity in the different sample sets stratified by assay.

Results: HPV prevalence was similar in the L1-based assays compared to E6/E7-based assays for all sample types. No significant differences were seen between the individual assays (Table 1). Invalidity rate varied between assays and ranged from 0% for EUROArray HPV test, 1.01% for Optiplex HPV Genotyping kit, 4.7% for RealTime HR-HPV Assay to 18.79% for Xpert HPV.

Conclusions: HPV target sequence (L1 or E6/E7) does not influence likelihood of HPV detection in high-grade and invasive cervical and non-cervical lesions.

Table 1

#0433

34 - Economics and modelling

ESTIMATING THE IMPACT OF USING AN MRNA HR-HPV ASSAY COMPARED TO DNA HR-HPV ASSAYS IN THE ENGLISH PRIMARY HPV CERVICAL SCREENING PROGRAMME

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Background/Objectives: The aim was to estimate the impact of using an mRNA high-risk human papilloma virus (HR-HPV) assay (Aptima® HPV Assay) versus a DNA HR-HPV assay in a hypothetical cohort of women aged 25-65 followed for 3 years as part of the NHS Cervical Screening Programme (CSP) in England for HPV primary screening (first call or routine recall testing).

Methods: A decision tree was created to estimate the total colposcopies and total costs for the cohort, assuming either primary HPV screening with either the mRNA (Aptima) or HC2 and cobas DNA HR-HPV assay. The total HPV and cytology tests, and number lost to follow-up for each cohort were also estimated. The model was parameterised with data from the CSP (2017/18) and the HORIZON study. Uncertainty analyses were conducted to test the robustness of results using alternative data sources, as well as conducting one-way, probabilistic, and scenarios analyses.

Results: Assuming a total cohort in one year of 2.25 million women in England, an estimated £11.3 million (95% CI £2.4 - £20.0 million) could be saved and 25,236 (95% CI 24,680-25,704) unnecessary colposcopies averted if Aptima mRNA assays are used instead of DNA assays. This would also yield an estimated 57,758 fewer unnecessary HR-HPV and 171,306 cytology tests performed. Even when alternative data sources were used in the model, model results indicated that using the mRNA assay generated cost savings and reduced testing in every scenario.

Conclusions: By choosing a more specific assay for HPV primary screening, cost savings and a reduction in unnecessary testing and procedures could be achieved. This would benefit women in the CSP and the NHS. These results are important to help inform organisations in choosing which assays to use as part of their screening programme, and results are likely to be generalisable to other countries.

#0738

8 - HPV testing

COMPARATIVE PERFORMANCE OF THE ALINITY M HR HPV ASSAY ON THINPREP, SUREPATH AND ALINITY M CERVI-COLLECT SPECIMENS

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Background/Objectives: Cervical cytology using ThinPrep (TP) or SurePath (SP) collection systems, and testing for high risk human papilloma virus (HR HPV) using a variety of approved commercial assays has dramatically reduced the incidence of cervical cancer. Abbott Molecular Inc. has developed the Alinity m HR HPV DNA assay and an Alinity m Cervi-Collect (CC) Specimen Collection Kit. The study objectives were to enroll 560 women attending a Colposcopy clinic and to proportionally collect cervical samples in ThinPrep, SurePath and Cervi-collect solutions to be tested by the Alinity m HR HPV assay in an automated Alinity instrument and/or cobas HPV assay in a cobas 4800 instrument (Roche Diagnostics).

Methods: Using commercial collection devices, 280 women provided TP and CC samples (Arm 1), 140 provided TP followed by SP (Arm 2) and 140 others had SP collected followed by TP (Arm 3). Cytology, cobas and Alinity were performed on TP and SP samples. CC and pre- and post cytology TP and SP samples were also tested by Alinity m HR HPV. Positive % agreement (PPA), negative % agreement (NPA), and overall % agreement (OPA) and Kappa statistics were calculated.

Results: OPA of Alinity and cobas was almost perfect in TP (94.2%; k 0.88) and SP (91.7%; k 0.82) and showed a strong correlation between the 2 HPV assays for the detection of HPV16 (OPA 98.1%) and HPV18 (OPA 99.4%). Comparing the three samples tested by Alinity demonstrated almost perfect agreement between TP and CC (94.6%; k 0.88) between TP and SP (93.8%; k 0.86), between TP pre- versus post- cytology (97.5%; k 0.96) and between SP pre- versus post- cytology (92.9%; k 0.85). Comparing Alinity and cobas according to cytological categories showed relatively equal HR HPV rates for negative cytology, ASCUS, LSIL and HSIL.

Conclusions: The Alinity m HR HPV assay showed almost perfect agreement to the cobas HPV test with TP and SP specimens. The Alinity assay showed consistent performance in CC, SP and TP samples. HR HPV positivity rates by Alinity and cobas were similar in all cytological scoring categories.

FC 14 - HPV screening (II)

#0482

9 - HPV screening

Quality Assurance of HPV tests and Triage Cytology: Lessons from Australia

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Background/Objectives: Australia has had an organised screening program based on conventional cytology for well over two decades. Commencing in December 2017 Australia changed to Primary High Risk HPV (hrHPV) testing with partial genotyping and cytologic triage for screening purposes. The screening interval was changed from 2 to 5 years and the age of commencement was changed from 20 years to 25 years at the same time. Quality Assurance of these tests is required to ensure test sensitivity and specificity is maintained. The component parts of quality assurance comprise internal quality control of the hrHPV testing andpartial genotypng, external quality assurance by means of surveys using known samples and numerical performance measures for all laboratories engaged in testing This presentation aims to demonstrate the strengths and weaknesses associated with these Quality Assurance components used in the Australian organised national cervical screening program.

Methods: The Quality Assurance Standards for Cervical Screening as promulgated by the National Pathology Accreditation Advisory Committtee (NPAC), the national agency responsible for setting laboratory standards of practice will be summarised. The methods of operation of the external quality assurance programs for hrHPV testing and partial genotyping along with the results of these surveys will be summarised. The methodologies utilised for calculating numerical performance measures including the use of Funnel Plots will be decribed and the confounding factors enumerated. The use of internal quality controls for each testing run by each laboratory will be described. The linkage of the internal quality control results to an independent database will be described.

Results: The results of these quality assurance activities will be demonstrated using the data that has been released into the public domain so far.

Conclusions: This presentation will show that tried and tested external quality assurance surveys similar to those utilised internationally have limitations most notably related to the sample size of the surveys compared to the sheer numbers of tests being performed by labortatories. The lack of a demonstrable link between what occurs in external surveys and what happens on a day to day basis is weakness that has to be acknowledged. The numerical performance measures for laboratories reporting HPV tests is beset with confounding factors that render them all but unusable. The linkage of internal quality assurance peroformance to what is effectively an independent national database is regarded as a ground breaking initiative when applied to cervical screening testing. This methodology has the potential to solve many of the problems associated with quality assurance of these tests and provide and efficient reliable means of ensuring consistent sensitivity and specificity of the hrHPV tests.

#0434

9 - HPV screening

Comparison of p16/ki67 dual staining and E6/E7 mRNA overexpression as triage test in HPV DNA-positive women: accuracy and prognostic value.

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Background/Objectives: The aim of the New Technology in Cervical Cancer 2 (NTCC2) study was to compare E6/E7 mRNA overexpression and p16/ki67 dual staining in terms of their accuracy and prognostic value in triaging HPV DNA-positive women.

Methods: Women were tested with HPV DNA test (Cobas 4800 [Roche] or Hybrid Capture 2 [Qiagen]). Those positive were triaged with cytology and tested for E6/E7 mRNA and p16/ki67. Women with positive cytology were referred to colposcopy, while those negative were randomised to immediate colposcopy or to 1-year HPV retesting. We report colposcopy referral (immediate and after 1-year HPV retesting), sensitivity, and positive predictive value for CIN2+ of cytology, E6/E7 mRNA, p16/ki67. For the latter two, we also report the ability to predict HPV clearance and CIN2+ regression. All lesions found within 24 months of follow up were included.

Results: Of the 40509 women recruited, 3147 (7.8%) were HPV DNA positive. Cumulatively, 174 CIN2+ were found; sensitivity was 94.4% (95%CI 89.1, 97.3) 75.2% (95%CI 68.1, 81.6), and 61% (95%CI 53.6-68.0) for mRNA, p16/ki67, and cytology, respectively. Immediate referral was 67.4%, 29.0%, and 25.6%, respectively. Overall referral was 78.6%, 65.3%, and 63.7%, respectively, and PPV was 8.3%, 9.55%, and 10.1%, respectively. Of the 2308 HPV-positive/cytology-negative women, relative detection in those randomized at 1-year retesting vs. immediate colposcopy suggests a -28% CIN2+regression (95% CI -57%, +20%). In women positive for E6/E7 mRNA or p16/ki67, CIN2+ regression was almost null, whereas in those negative it was -76% (95% CI -97, +111) and -42% (95% CI -73%, +27%), respectively. HPV clearance at 1 year was 1.9 (95% CI 1.7-2.2)and 1.9 (95%CI 1.5-2.5) times higher in those who were mRNA and p16/ki67 negative, respectively.

Conclusions: P16/ki67 showed good performance as triage test for HPV DNA-positive women. mRNA E6/E7 overexpression showed too high a positivity rate among HPV DNA-positive women to be efficient as triage test, but when negative it showed a good prognostic value to identify infections at high probability of clearance and regressive CIN2+.

References: *The following are components of the New Technologies for Cervical Cancer 2 Working Group: Regione Lazio: Alessandra Barca, Francesco Quadrino. IRCCS Regina Elena National Cancer Institute, Rome: Maria Benevolo, Francesca Rollo. AUSL Reggio Emilia: Paolo Giorgi Rossi, Pamela Mancuso, Francesco Venturelli, Gabriele Carlinfante, Teresa Rubino. ISPRO Florence: Francesca Maria Carozzi, Simonetta Bisanzi, Massimo Confortini, Carmelina Di Pierro, Giulia Fantacci, Anna Iossa, Alessandra Mongia, Cristina Sani GiamPaolo Pompeo, Donella Puliti, Andrea Baldini . CPO and Centro Unico di Screening Cerv Vag, Turin: Guglielmo Ronco, Raffaella Rizzolo, Anna Gillio Tos, Laura De Marco, Elena Allia. APSS, Trento: Teresa Pusiol, Mattia Barbareschi, Emma Bragantini. USL Umbria1, Perugia: Basilio Passamonti, Daniela Gustinucci, Simonetta Bulletti, Elena Cesarini, Maria Donata Giaimo. Este Monselice (PD): Gabriella Penon, Alessandra Bertazzo, Laura Toniolo, Angelo Farruggio, Natalina Marchi; Istituto Oncologico Veneto IOV-IRCCS: Annarosa Del Mistro, Helena Frayle, Silvia Gori; Registro Tumori del Veneto: Manuel Zorzi; UOC Screening e VIS: Elena Narne, Anna Turrin.

#0284

9 - HPV screening

TRIAGING HPV POSITIVE WOMEN WITH LOW-GRADE CYTOLOGY: EVIDENCE FROM 10 YEAR FOLLOW-UP OF THE ARTISTIC TRIAL COHORT

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Background/Objectives: New HPV infections often exhibit low-grade dyskaryosis but are likely to clear without intervention. Screening programmes in the UK and Europe refer these women to colposcopy without delay, but is this the best management for these women?

Methods: The ARTISTIC trial cohort (N=24,510) were recruited in Manchester in 2001-03 and were traced for CIN3 and cancer incidence through national registration until December 2015. Long-term CIN3 risks associated with different triage strategies for HPV positive women with borderline and low-grade cytology were estimated.

Results: The 10 year cumulative risk of CIN3+ was much higher for women with HPV16/18 infection at baseline (19.4%, 95%CI:15.8-23.8) than for those with other HPV types (7.3%, 95%CI:5.4-9.7). Sixty percent of the women (568/944) had non 16/18 HPV infections, of which 40% cleared after 6 months. Among the 110 women with a new HPV infection, the 10 year cumulative CIN3+ risk was 6.4% (95%CI:3.1-12.9), approximately half the risk estimated from baseline (12.1%, 95%CI:10.2-14.4).

Conclusions: Immediate referral of all HPV+ women with borderline or low-grade cytology will not be cost-effective, particularly in women who have tested HPV negative in the previous round of screening. The CIN3 risk is confined to women with persistent type-specific HPV so partial genotyping test assays identifying HPV16/18 as a minimum are essential for efficient risk stratification. Immediate referral to colposcopy for HPV+ women with borderline or low-grade cytology may be unnecessary and women can safely be retested to identify those with persistent HPV. Prevalent cancers, including all 10 in ARTISTIC, almost always present with high grade cytology. Of the HPV+ women with low-grade dyskaryosis referred to colposcopy in England in 2017-18, 38% showed normal colposcopic appearance and were returned to 3 year recall and only 0.12% were diagnosed with cervical cancer. The minimal risk of invasive cancer that has progressed beyond stage 1A must be weighed against the advantages for patients and savings in clinical costs of reducing the number of referrals to colposcopy.

#0512

9 - HPV screening

HPV Screening and reproducibility of Triage Cytology : revision of negative Triage Pap test from women with Cin2+ lesion at 1 year follow-up

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Background/Objectives: In HPV screening Program , the aim of triage cytology is to increase the specificity of the HPV-HR test, used as primary test in cervical cancer screening, selecting the HR-HPV+ women who require colposcopy referral from those with negative cytology to be checked again after 1 year. The aim of this study is the review of negative triage Pap test in women with CIN2+ lesions at 1-year follow-up and to evaluate the reproducibility of negative triage cytology in a screening context.

Methods: A set of 192 negative triage cytology (period 2013-2015) were retrieved and independently interpreted by 5 cytologists. These slides were reviewed blinded to final result at 1-year follow-up: 64 CIN2+, 64 CIN1 and 64 didn't develop lesions at 12-month control. Kappa values were obtained from the comparison between individual cytological results at revision and majority diagnoses with initial diagnoses.

Results: The review didn't confirm the initial cytological result only in 13/192 (6.7%) : 9/64 cases of CIN2 + (14.1%), 1/64 cases of CIN1 (1.5%) and 3/64 negative cases at 1-year control (4.7%) between 64 cases with CIN2 + at the 1-year follow-up the review showed that in most of these case only very few or minimal cytological atypical cells alteration and the K value between the 5 readers showed a moderate agreement (from 0.33 to 0.56).

Conclusions: In HPV screening, the Pap test changes its role because it must increase the specifity of HPV test. So this study showed a high reproducibility of negative triage cytology in HPV screening but it important to introduce systematically internal quality control . Based on the results of this review, each laboratory should evaluate the opportunity to include triage cytology re-screening as internal quality control.

#0498

9 - HPV screening

THE POSSIBLE ROLE OF CYTOLOGY AT 12-MONTH RECALL IN PRIMARY CERVICAL SCREENING WITH HR-HPV

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Background/Objectives: In Florence HPV Cervical cancer screening program started in 2013 and invited all resident women aged 34-64 years. According to the Italian primary cervical screening algorithm, HPV+ women with abnormal cytology are referred immediately to colposcopy while HPV+ women with normal cytology are invited to repeat HPV DNA testing after 12 months. Persistent HPV+ women at 12-month recall are then referred to colposcopy. High persistence of HPV+ tests at 12-month recall overloads colposcopy. The aim of this study is to evaluate an alternative screening protocol at 12-month recall to minimise unnecessary referral of HR-HPV+ persistent women, evaluating the role of cytology alone or combined with HPV16/18 genotyping.

Methods: The study analyses the results of women that at enrolment, between 2013 and 2019, had a screening HPV test positive with cytology triage negative and persisted HPV+ at 12-month recall. All results at 12-month recall have been compared with colposcopy/histology.

Results: About 140,000 women participated to the HPV test primary screening (2013-2018). The mean positivity rate was 7%. About 6200 HPV+ and cytology triage negative women were recalled after 12 months and 5133 (82.7%) repeated HPV test: 57.6% (2959) had a HR-HPV persistent infection. Colposcopy results are available for 2647 (89.5%) women and 8.9% (237/2647) had a CIN2+. Cytology results are available for all women sent to colposcopy (2647) while HPV16/18 partial genotyping is available only for women tested with CobasÒ 4800 HPV (1770). Cytology was negative in 75.9% (2008/2647) and, among them 5.5% had a CIN2+ lesion. Among women with abnormal cytology (ASC-US+), 19.9% had a CIN2+ lesion (p. <0.0001) (figure a). Cytology at 12-month recall was able to identify only 53.5% (127/237), even if it saved 76% (2008/2647) of colposcopies. HPV 16/18 partial genotyping was able to identify 34.2% (25/73) of CIN2+ lesions among HPV+/normal cytology Thus, at 12-month recall cytology combined with HPV16/18 genotyping could be able to identify 68% (102/150) of the CIN2+ lesions, even if it saved 58% (1021/1770) of colposcopies.

Conclusions: These data suggest that adding at 12-months-recall a triage test decreases the sensitivity, so at the moment it is advisable to maintain the current protocol sending to colposcopy all women with persistent HPV infection. At the same time, the low VPP of the actual protocol suggest that is crucial to identify biomarkers able to select the population at greatest risk of CIN2+ lesion among HPV+/normal cytology women at 12-month recall.

#0384

14 - Screening methods

DUAL STAINING FOR P16/KI-67 TO DETECT HIGH-GRADE CERVICAL LESIONS: RESULTS FROM THE SCREENING TRIAGE ASCERTAINING INTRAEPITHELIAL NEOPLASIA BY IMMUNOSTAIN TESTING (STAIN-IT) STUDY

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Background/Objectives: Testing for the presence of cervical epithelial cells simultaneously co-expressing the tumor-suppressor protein p16INK4a (p16) and the proliferation marker Ki-67 using a dual immunocytochemical staining protocol has been shown to be a promising triage tool for abnormal cytology results. We compared the clinical performance of p16/Ki-67 dual-stained cytology and HPV genotyping, via different algorithms, alone, or in combination with cytology, to identify cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in women referred to colposcopy at three university-affiliated hospital clinics.

Methods: The STAIN-IT study included 492 (134 normal, 130 CIN1, 99 CIN2, 115 CIN3, 6 CIN2/CIN3, 8 cancers) randomly selected specimens out of 1158 specimens with valid conventional cytology, HPV and biopsy results. Cervical specimens, collected by gynecologists, were transferred to PreservCyt solution and tested for the presence of high-risk HPV, hrHPV (cobas® 4800 HPV Test). Dual staining (CINtec® PLUS assay; Roche Laboratories) was retrospectively performed, and each slide was read by a cytologist and confirmed by two pathologists. Slide readers were blinded to cytology, biopsy, and genotyping results. Accuracy (correct classification rate), sensitivity and specificity (restricted to lesion-free women) and their 95% confidence intervals (in parentheses below) of p16/Ki67 dual-staining to detect CIN2+ were calculated and compared with other screening tests available for the same women (HPV testing and genotyping, cytology, and combinations), overall and stratified by age (≤30, >30 years).

Results: hrHPV and HPV16/18 positivity were detected in 321 (65.2%) and 139 (28.3%) women, respectively. The overall positivity rate for dual staining was 56.7%; increasing with histological severity from 30.6% in normal, 41.5% in CIN1, 72.7% in CIN2, 87.8% in CIN3 to 87.5% in cancer cases. Both dual-stained cytology and hrHPV positivity had similar accuracy [71.8% (67.6-75.7)] in predicting CIN2+; superior to cytology [ASC-US: 65.0 (60.6-69.3); LSIL: 66.7 (62.3-70.8)]. Dual staining alone had lower sensitivity [80.7% (75.0-85.6) vs. 89.9% (85.3-93.5)] and higher specificity [69.4% (60.9-77.1) vs. 64.9% (56.2-73.0)] for CIN2+ compared with hrHPV testing. Combining dual-stained cytology with an ASC-US abnormality threshold, sensitivity increased to 96.1% (92.6-98.2) whereas specificity decreased to 40.3% (31.9-49.1). Corresponding values considering an LSIL threshold were 91.7% (87.3-94.9) and 53.0% (44.2-61.7). Comparable performance patterns were observed among women under and above 30 years.

Conclusions: Dual-stained cytology and HPV testing had similar performance in predicting CIN2+, although it could improve slightly the specificity of detection of high-grade lesions.

#0230

9 - HPV screening

APPROACHES TO TRIAGE OPTIMIZATION IN HPV PRIMARY SCREENING: EXTENDED GENOTYPING AND P16/KI-67 DUAL-STAINED CYTOLOGY - RETROSPECTIVE INSIGHTS FROM ATHENA

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Background/Objectives: The objective of this study was to assess the performance of different triage strategies for high-risk HPV (hrHPV)-positive results utilizing either extended genotyping or a p16/Ki-67 dual-stained cytology (DS) approach, with or without partial genotyping.

Methods: A subset of women with hrHPV infections participating in the ATHENA study were analyzed to determine the number of cervical intraepithelial neoplasia grade 3 or worse (≥CIN3) cases detected, and the absolute risk for ≥CIN3 of each genotype. A clinical utility table was constructed to compare the impact of different triage strategies.

Results: 2339 women with single-genotype hrHPV infections were identified. Among these were 171 ≥CIN3 cases. The FDA-approved algorithm (HPV16/18 positive, or 12-other hrHPV positive and Pap positive, i.e. ≥ASCUS) for primary HPV screening detected 132/171 (77.2%) ≥CIN3 cases and required 964 colposcopies (colposcopies per ≥CIN3 ratio: 7.3). An approach that uses DS instead of cytology in the FDA-approved algorithm detected 147/171 (86.0%) ≥CIN3 cases, requiring 1012 colposcopies (ratio: 6.9). Utilizing DS for triage of all hrHPV-positive women identified 126/171 (73.7%) ≥CIN3 cases, requiring 640 colposcopies (ratio: 5.1). A strategy that detected HPV16/18/31/33/35+ captured 130/171 (76.0%) ≥CIN3 cases, requiring 1025 colposcopies (ratio: 7.9).

Conclusions: Inclusion of additional genotypes resulted in greater disease detection at the expense of higher colposcopy ratios. Substituting cytology with a DS triage approach improved disease detection and the colposcopy detection rate. Further reduction of colposcopy rates can be achieved by using DS without partial genotyping. Extended genotyping strategies can identify a comparable number of cases but require an increased number of colposcopies.

#0471

9 - HPV screening

COMBINED USE OF CYTOLOGY, p16 IMMUNOSTAINING AND GENOTYPING FOR TRIAGE OF WOMEN POSITIVE FOR HIGH RISK HUMAN PAPILLOMAVIRUS AT PRIMARY SCREENING

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Background/Objectives: HPV testing is a very sensitive method of primary cervical screening, but suffers from low specificity. Triage tests which improve specificity, but still maintain high sensitivity are needed.

Methods: Women enrolled in the experimental arm of phase 2 of the NTCC randomised controlled cervical screening trial were tested for high risk human papillomavirus (hrHPV) and referred to colposcopy if positive. hrHPV positive women also had HPV genotyping (by PCR with GP5+/GP6+ primers and reverse line blotting), immunostaining for p16 overexpression and cytology. We computed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different combinations of tests, and determined potential hierarchical ordering of triage tests.

Results: 1091 HPV positive women had valid tests for cytology, p16 and genotyping, of which, 92 were histologically CIN2+ and 40 CIN3+. The PPV for CIN2+ was >10% in hrHPV positive women with HSIL+ (61.3%), LSIL+ (18.3%) and ASCUS+ (14.8%) cytology, p16 positivity (16.7%), and hierarchically for infections by HPV33, 16, 35, 59, 31 and 52 (in decreasing order). Referral of women positive for either p16 or LSIL+ cytology gave a sensitivity of 97.8% for CIN2+, and woman negative for both of these had a 3-year CIN3+ risk of 0.5%. Similar results were seen for women either p16 or HPV16 positive.

Conclusions: hrHPV+ women who were negative for p16 and LSIL+ had a very low CIN3+ rate in the next three years. Recalling them after that interval and referring those positive to either test to immediate colposcopy appears to be an efficient triage strategy.

#0462

9 - HPV screening

PERFORMANCE OF HPV16/18 GENOTYPING AS A TRIAGE TEST OF HPV POSITIVE WOMEN IN LATIN AMERICA

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Background/Objectives: Persistent infection with oncogenic HPV is the main cause of cervical cancer. HPV prevalence among women of screening age is about 13%. Referring HPV positives to colposcopy can cause unnecessary anxiety and overloading of colposcopy clinics. There is a need for triage tests to select HPV positive women at high risk of cervical precancer and cancer. Genotyping for HPV16 and HPV18, responsible for about 70% of cervical cancer can be used as triage and reduce the number of women referred to colposcopy with sensitivity at least as good as currently used triage cytology. The ESTAMPA study is recruiting 50,000 women, 30 to 64 years old in nine countries of Latin America (LA) to evaluate cervical cancer screening by HPV and triage methods for HPV positive women.

Methods: Women from five ESTAMPA centers (Costa Rica, Argentina, Colombia - Bogota and Apartado, and Paraguay) are being screened with the COBAS PCR test, which provides individual results for HPV16 and HPV18 and grouped results for other 12 high-risk HPV types. All HPV positives are referred to colposcopy with biopsy collection and treatment as appropriate. The outcome for this analysis was CIN2+ confirmed by local histology (expert review underway). We evaluated the performance of HPV16 and HPV18 genotyping as triage of HPV positive women for CIN2+ detection among 11,406 women HPV screened by COBAS.

Results: A total of 1537 were hrHPV positive (HPV prevalence: 13%; 95% CI 12.9-14.1). Of them, 94% (1377) had already attended colposcopy and 69 of them had histologically confirmed CIN2, 156 CIN3, and 8 cancer. Of those attending colposcopy, 288 women were positive for HPV16, 111 for HPV18, and 11 for both types (HPV16/18 positivity: 29.8% (95% CI 27.4-32.2). The sensitivity of HPV16/18 genotyping was 57.5% (95% CI 51.1-63.7) and the specificity 76% (95% CI 73.3-78.3) for CIN2+ detection. Sensitivity was higher in women over 50 years. In comparison, cytology without knowledge of HPV had a sensitivity of 39.4% (95% CI 24.7-56.3), (p for the difference = 0.0005). Positive predictive value of HPV16/18 was 33% (95%CI 28.3-37.4) compared to 10% of women positive for any of the other 12 hrHPV, suggesting that they could be managed differently, for instance with repeat HPV testing at 12-18 months.

Conclusions: Triage of HPV positive women by HPV 16/ 18 genotyping reduced colposcopic referral and had better sensitivity than cytology without knowledge of HPV status. Performance of cytology with knowledge of HPV status is under evaluation, but genotyping can be particularly useful in the context of screening programs based on self-collection, which does not allow cytology in the same specimen.

#0240

8 - HPV testing

CLINICAL VALIDATION OF BROOM VS BRUSH/SPATULA COLLECTED CYTOLOGY FOR ASC-US TRIAGE BY HPV TESTING USING A MOLECULAR HPV TEST: RESULTS FROM THE IMPACT TRIAL

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Background/Objectives: As one of the objectives of the IMPACT (IMproving Primary screening And Colposcopy Triage) trial, we evaluated the clinical performance of a molecular HPV test in samples collected with a cervical broom from women 25 years or older with atypical squamous cells of undetermined significance (ASC-US).

Methods: Women (N = 35,263) were recruited in the United States during routine screening, and liquid-based cytology and HPV testing were performed. The specimen was randomized to be collected using a broom-type device for approximately half of the subjects and a brush/spatula for the other half as a control.

Results: The ASC-US prevalence was 6.5% (2,270/34,819), and thereof 1,921 women underwent colposcopy with valid results. For the detection of cervical intraepithelial neoplasia (CIN) grade 3 or worse, the cobas 4800 HPV Test with broom demonstrated comparable sensitivity to the cobas 4800 HPV Test with brush/spatula [sensitivitybroom 87.5% (95% CI: 64.0%, 96.5%), sensitivitybrush/spatula 83.3% (95% CI: 60.8, 94.2)]. It also demonstrated comparable specificity for CIN3 or worse lesions [specificitybroom 66.3% (95% CI: 63.1%, 69.3%), specificitybrush/spatula 67.1% (95% CI: 63.9, 70.1)].

Conclusions: The above data support the clinical validation of the cobas 4800 HPV Test for ASC-US triage in samples collected with both a cervical broom device and an endocervical brush/spatula in PreservCyt. Results provide evidence for the safety and effectiveness of the cobas 4800 HPV Test in situations when clinicians prefer to use a cervical broom collection device.

FC 15 - Self-sampling (II)

#0451

10 - Self-sampling

HOME SELF-SAMPLING TO ENHANCE UTERINE CERVICAL CANCER SCREENING, VAGINAL OR FIRST-VOID URINE ? A COMPARATIVE MULICENTRE STUDY.

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Background/Objectives: To increase patient's compliance with cervical cancer (CC) screenings, home self-sampling for Human Papillomavirus (HPV)-DNA detection could be an alternative to clinician sampling. Home self-sampling can reduce screening difficulties, CC incidence and mortality. The aim of this French prospective multicentre PapU APV study was to evaluate self-collected vaginal (SCV) and first-void urine (FVU) for HPV-DNA screening.

Methods: From 2014 to 2015, 461 women were invited to realize the two self-samples; among them, 176 were seen in gynecology units from Brest, Landerneau and Carhaix hospitals (referral group 1) and 285 were from other units, visitors and employees of Brest university hospital (general population group 2). Vaginal and fist-void urine samples were send to the Brest virology lab for HPV-DNA quantification by real-time PCR and genotyping, with a signed consent and a questionnaire for sampling evaluation and their preference. Cytological results were also recorded.

Results: High-risk HPV-DNA prevalence was similar in the 2 groups and in SCV and FVU (respectively 14.1% and 11.5%, p=0.45). Good agreement with the two self-sample was observed (80.3%) with a moderate concordance Kappa rate (0.51). Compared to cytological results (n=303), sensitivity and specificity rates for high-grade lesion detection were similar with SCV and FVU (respectively 100% vs 100%, p=1 and 67.5% vs 63.2%, p=0.64). Preference was significantly higher for FVU than SCV (respectively 40.5% vs 13.3%, p<0.001).

Conclusions: The first-void urine home self-sampling was showed in our multicentre study to be as efficient to detect high-grade lesions as self-vaginal sampling but highly preferred in referral and general population groups. We could propose first-void urine self-collect HPV as a primary CC screening strategy for difficult to reach women as evaluated in our PapU29 study in 15471 women. Grants from the French Ligue contre le Cancer

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#0684

10 - Self-sampling

Determination of the optimal first-void urine collection volume for the detection of viral and host biomarkers, and evaluation of an internal control

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Background/Objectives: To date, screening in most EU countries is based on cytology, which requires a physician-taken cervical scrape and is challenged by low sensitivity (30% false-negatives) and high non-attendance (63% EU coverage). The goal of the CASUS project is to develop the first fully molecular integrated cervical cancer screening approach, based on first-void (FV) urine as an easily accessible and non-invasive source of biomarkers. This study focused on the development of next generation Colli-Pee FV urine devices to determine the optimal volume for the detection of viral and host biomarkers, and their clinical performance. The validation of an appropriate control to monitor sample transport, storage and extraction was done in parallel.

Methods: For this study, 25 women (at least 18 years old) diagnosed with a high-risk (hr) HPV infection in the past six months, provided three consecutive FV urine samples with a minimum time interval of 2h. Each sample was collected at home, using Colli-Pee devices with collector tubes that differ in size, prefilled with preservative (Urine Conservation Medium (UCM)) and spiked with an internal process control in a 2:1 urine preservative ratio. This allowed us to collect an average of 2.67 mL urine, 6.67 mL urine and 13.33 mL urine in 4 mL, 10 mL and 20 mL tubes respectively. On each sample, DNA extraction was performed followed by real-time RT-PCR to obtain Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and internal control threshold cycle (Ct) values. The internal control needs to confirm presence of sufficient preservative, to demonstrate that the extraction was well performed and finally show that no degradation of biomarkers took place.

Results: Results from the three samples collected by 25 different hrHPV positive women (n=75) will be presented at the EUROGIN conference. These include (1) comparison between collection of different FV urine volumes, (2) comparison of four different extraction methods performed on the 20 mL FV urine sample and (3) evaluation of the internal control.

Conclusions: The results of the first objectives in the CASUS study regarding the determination of the optimal FV urine volume to be collected and evaluation of the internal control will be the first step towards development of the first fully molecular integrated cervical cancer screening approach based on first-void urine.

#0078

10 - Self-sampling

ACCURACY OF HPV TESTING ON VAGINAL AND URINE SELF-SAMPLES TO PREDICT RESIDUAL/RECURRENT DISEASE IN WOMEN TREATED FOR HIGH-GRADE CERVICAL DYSPLASIA (TEST OF CURE)

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Background/Objectives: HPV testing on self-collected samples has been demonstrated to be a valid and more acceptable alternative to improve coverage rates in cervical cancer screening. As HPV DNA testing has been shown to be more sensitive in predicting residual/recurrent disease in women treated for high-grade cervical dysplasia, self-sampling may also prove to be useful in a test of cure setting, reducing post-treatment visits and patient's lost-to-follow-up. This ongoing study aims to investigate the accuracy of HPV testing on vaginal and urine self-samples as compared to clinician-collected cervical samples (gold standard) in women referred to colposcopy for an abnormal cytology result, requiring conization and subsequent follow-up examination.

Methods: Self-collected vaginal, urine and physician administered cervical samples, were collected from women attending the Colposcopy Clinic, San Gerardo Hospital (Monza, Italy) and followed-up after conization. All samples were extracted using NucliSENS easyMAG and HPV detection carried out using AnyplexII HPV28.

Results: Presently, 180 women have been enrolled at colposcopy. Thirty-six of these (36/180, 20%) were treated by conization and 14 have returned for a 6 months follow-up visit. Preliminary results have shown 94% (34/36) high-risk HPV positivity at colposcopy, with HPV16 and HPV31 being the most frequent types detected. At follow-up, the majority of women (9/14, 64%) resulted hrHPV DNA negative from the analysis of cervical sample, as expected. The remaining women continue to be HPV infected with at least one of the HPV types detected at baseline. A very good HPV test concordance was observed between vaginal and urine self-samples as compared to clinician-collected cervical samples, both at colposcopy and at follow-up.

Conclusions: Preliminary data demonstrate promising results for the use of urine and vaginal self-collected samples in a test of cure setting, allowing for fewer post-treatment visits and avoiding unnecessary cytologies to predict residual/recurrent disease.

#0595

10 - Self-sampling

HPV DETECTION IN URINE SAMPLES COLLECTED USING COPAN'S URISPONGETM VERSUS CLINICIAN-COLLECTED CERVICAL SAMPLES.

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Background/Objectives: Urine collection is a non-invasive sampling procedure, especially in pregnant women, for HPV screening both at point of care or home setting. Copan UriSpongeTM consists of a leak-proof screw-cap tube with attached a plastic stick with 3 sponges containing preservative salts, to absorb and retain urine samples, prevent bacterial overgrowth during transport and allowing for microbial detection by culture and/or molecular assays. The objective of this study was tocompare UriSpongeTM first catch urine (FCU) to clinician-collected cervical samples (CS) for the detection of HPV with the AnyplexIITM HPV28 assay (Seegene).

Methods: Urine and cervical samples were obtained from 104 women with a recent diagnosis of cervical dysplasia, attending the Colposcopy Centre of San Gerardo Hospital, Monza, Italy. FCU were collected in sterile containers, CS were collected using the L-Shaped Endo/Esocervical FLOQSwab® and resuspended in 20ml ThinPrep solution (Hologic).In the laboratory, two or three separate UriSpongeTM were immerged in each urine container until fully saturated. Preliminary results on UriSpongeTM stability at room temperature (RT) after 1-week (n=60) and 4-weeks (n=30) were also evaluated. Nucleic acids were extracted from 1ml of FCU and CS using NucliSENS easyMAG (bioMérieux). HPV detection was performed using AnyplexIITM HPV28 Assay. Sample cellularity was evaluated by an in-house quantitative real-time PCR assay detecting human CCR5 gene.

Results: In the 104 women tested, CS had an HPV positivity rate of 63% for HR and 44.2 % for LR while FCU had a positivity rate of 66% for HR and 52% LR. The UriSpongeTM (N=60) samples 1-week RT stability positivity rate was 66.7% for HR and 45% for LR while the UriSpongeTM (N=30) samples 4-weeks RT stability positivity rate was 53.4% for HR and 36.4% for LR. A good results concordance was obtained for HR HPV detection in urines as compared to cervical, with HPV HR types 16, 18, 51 and 31 being the most frequently detected. Comparable cellularity was demonstrated in both sample types with mean values of 2.09E+06 and 3.16E+06 cells/sample for FCU and CS respectively.

Conclusions: Data obtained in this study confirmed a good concordance in HR HPV detection in both CS and FCU collected using UriSpongeTM. Cellularity of samples collected with UriSpongeTM and L-shape Endo/Esocervical FLOQSwab® collection devices showed comparable results. Moreover UriSpongeTM RT stability was good after 1-week with a minor loss after 4-weeks. In conclusion UriSpongeTM is easy to use, not bulky, can be conveniently shipped by mail and costs less than other urine collection devices, so its use can be advocated to increase women's participation to cervical cancer screening programs.

#0511

10 - Self-sampling

COMPARISON OF REALTIME HIGH RISK HPV RESULTS FROM VAGINAL SELF-SAMPLED SWABS AND PHYSICIAN-COLLECTED PRESERVCYT SAMPLES

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Background/Objectives: Vaginal self-sampling for high risk HPV (hrHPV) DNA testing using PCR-based tests validated for primary cervical cancer screening has shown acceptable performance in a previous meta-analysis. Evaluating specific self-collection devices using standardized protocols for hrHPV testing of self-sampled specimens from screening non-attenders prior to implementation in routine cervical cancer screening is essential. Objective Within the VALHUDES framework, this study aims to investigate whether hrHPV DNA testing on self-collected dry vaginal swab samples identifies infection at clinically relevant levels by comparison to physician-collected cervical scrape samples (reference).

Methods: 402 matched pairs of swab (Multi-Collect swab; Abbott) and reference samples (Cervix Brush Combi; Rovers, Oss, The Netherlands) collected in PreservCyt medium from women (25-64 years of age) referred for colposcopy in 5 Belgian centres between January 2018 and August 2019 were tested side-by-side with the RealTime High Risk HPV assay (Abbott GmbH, Wiesbaden, Germany) on the m2000 System. Swab samples were considered to be hrHPV positive using the clinical threshold determined by the manufacturer for physician-collected LBC samples. HrHPV DNA detection rate per sample type and concordance of hrHPV results observed with both sample types were calculated.

Results: The overall hrHPV DNA detection rate in swab samples was 64.2% versus 56,7% in matched reference samples. The overall agreement of hrHPV DNA results on both sample types was 86.6% (k: 0,72 [95%CI: 0.65 - 0.79]). Considering "HPV16', "HPV18' and "Other HR-HPV' separately, the agreement was 95.5%, 98.0%, and 87.3%, respectively. Sensitivity and specificity of the swab protocol versus reference (94.7% [95%CI: 91.8%-97.6%]; 75.9% [(95%CI: 69.5%-82.2%]), rendered false positive and false negative rates of 24.1% and 5.3%, respectively.

Conclusions: Our results indicate a higher overall hrHPV DNA detection rate in self-collected vaginal swab samples compared to physician-sampled cervical samples and "good' concordance of hrHPV results from both sample types, are consistent with previous reports on other collection devices. For HPV16 and HPV18 "excellent' concordance was observed. Planned future assessment of hrHPV results versus clinical patient status will show whether higher HPV detection rates result in accurate disease prediction.

#0686

12 - Molecular markers

Non-invasive methylation test to detect cervical pre-cancer in self-collected vaginal and urine specimens.

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Background/Objectives: The implementation of HPV testing as a primary screen will soon become the norm worldwide. Because HPV testing is a very sensitive method, but not specific enough, the choice of an appropriate triage strategy for hrHPV positive women will be one of the future key issues facing the cervical screening community. Clinician taken samples are the gold standard but self-sampling may be a useful alternative for women not able or wishing to undergo examination. Collection of a urine sample offers a simple, non-invasive option. It has been shown that the sensitivity for detecting CIN2+ from HPV DNA testing from urine to only be slightly lower than clinician taken cervical samples (88.3% vs 94.5%) (Cuzick et al., 2017).We have developed a triage classifier (S5) for the detection of CIN2+, based on DNA methylation of HPV16, HPV18, HPV31 and HPV33 combined with the human gene EPB41L3 (Brentnall et al., 2015). The purpose of this project is to test this classifier on two non-invasive specimens: a self-collected vaginal sample and urine. We aim to assess whether S5 can identify women who are CIN2+ using self-collected samples.

Methods: Women attending the colposcopy clinic at The Royal London Hospital as a consequence of abnormal screening cytology and/or a positive HPV result were recruited as part of the "Self-sampling for vaginal HPV: Predictors 5.1' study. 503 women provided a urine sample using the Colli-PeeTM device with UCM storage buffer of which 300 women provided self-collected vaginal samples from FLOQswab (Copan) resuspended in PreservCyt medium. DNA was extracted and bisulfite conversion was carried out followed by pyrosequencing assays for the 6 S5 markers. Average methylation was calculated for each marker and the S5 score calculated.

Results: S5 showed a good and statistically significant separation between <CIN2 and CIN2+ samples for both urine and vagina self-samples (Mann Whitney test, p=<0.0001). The area under the ROC curve (AUC) was 0.7254 (CI: 0.667 to 0.7838, p=<0.0001) for urine samples and 0.7388 (CI: 0.6685 to 0.8091, p=<0.0001) for vaginal self-samples. At the pre-defined cut-off of 0.8, the sensitivity for urine samples was 66% and specificity 72% and vaginal self-samples was 71% and specificity 68%.

Conclusions: We demonstrated that S5 can be successfully amplified in urine and vaginal self-collected samples and that the classifier is able to correctly identify most of the CIN2+ women. Self-sampling will have an impact on both low and middle-income countries with limited access to effective screening programme and non-attended in high income countries.

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#0339

10 - Self-sampling

HASCO STUDY PROTOCOL: GERMAN PILOT STUDY FOR SYSTEMATIC HPV SELF SAMPLING FOR NON-RESPONDERS

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Background/Objectives: In this pilot study we will evaluate a systematic approach towards human papillomavirus (HPV) self-sampling for non-responders to the German cervical cancer screening program. In 2020, Germany will switch from opportunistic cytology screening to an organized system with co-testing in 3-yearly intervals. In the past, the participation rate was around 70% in a time frame of three years. The non-participators are at higher risk to develop cervical carcinoma. Previous studies have shown an improving number of patients participating when being re-invited. The willingness to participate in self sampling programs is even higher. Based on this information, the Hannover Self-Collection study was designed to examine the response rate and practicability of a systematic self-sampling approach.

Methods: 20.000 women aged 30 to 65 years living in the city and region of Hannover, Lower Saxony are randomly included. 10.000 women directly receive a self-sampling kit, the other 10.000 a letter of information and option to participate in the study (opt-out vs. opt-in strategy). Stratifications will be made by age (7 cohorts) and area of living (city vs rural). Women tested positive for high-risk HPV (PCR-based HPV assay) are prompted to get a cytological smear by their gynecologist. Women with normal cytology will be re-checked after 6 months. Suspicious cytology results lead to an immediate colposcopy. Further treatment will be performed according to the German S3-guideline prevention of cervical cancer.

Results: We designed a prospective randomized study to primarily examine: I) the participation rate (opt-out vs. opt-in model), II) the compliance after a positive HPV test, III) the comparison between two self-sampling gadgets, IV) triaging the samples by new DNA-methylation tests.

Conclusions: To get hold of non-responders to cervical cancer screening programs, self-sampling for HPV is a promising option. Aim of this study is to generate an overall recommendation to improve cervical cancer screening in Germany, especially for non-responders. This study is supported by Deutsche Krebshilfe.

#0567

10 - Self-sampling

LADYMED HPV TEST: A NEW HOME-BASED SELF-SAMPLING SERVICE TO INCREASE CERVICAL CANCER SCREENING PARTICIPATION

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Background/Objectives: Self-sampling for High-Risk HPV testing could be a valuable solution to increase cervical cancer screening coverage1,2. The organized cervical cancer screening in Italy reaches a three-year population coverage of 46,8% to which adds up to a 32,4% of women that undergo preventive Pap-test or HPV test by personal initiative. The remaining 20,8% of women never undergo to the cervical screening or participated only one time in their life3,4. In this context, we validated a new service (LadyMed HPV TestTM) that provides a vaginal FLOQSwabs® for home self-collection (Copan), a shipping service of the swab to a certified lab hub, HR-HPV analysis with HPV SelfyTM (a PCR-based test that targets and genotypes 14 High-Risk Human Papillomavirus, Ulisse BioMed)and a web app for user's registration and results delivery.

Methods: Women aged 20-65 years, who attended to the "Policlinico Univeristario campus Biomedico" (Rome, Italy) for a gynecologist visit, were invited to participate to this clinical study. The study was conducted in accordance with Helsinki Declaration (ethical approval n.56/18, 24/07/18). Women, who provided the informed consent, were asked to perform three different sampling: a physician-collected vaginal specimen using a sterile dry flocked swab (FLOQSwabs®, Copan); a physician-collected cervical brush rinsed into a ThinPrep® vial; and, at the end of the visit, women received a home HPV vaginal self-collection kit (containing a FLOQSwabs®, sampling and kit activation instructions and envelopes for sample shipping) to use alone at home at later time. Cervical brush samples were analysed using the HPV genotyping test CLART® HPV2 (Genomica) and self- and clinician-collected flocked swabs using HPV SelfyTM genotyping test (Ulisse BioMed). Self-sampling performance was compared to the conventional cervical brush; self- and clinician-collected vaginal flocked swabs instead, were useful to evaluate women ability to perform correctly the self-sampling procedure at alone home.

Results: Agreement between the HPV SelfyTM and CLART® HPV2 was 92%: 92,7% (95% CI: 0,869 - 0,964) for clinician-collected flocked swabs (Cohen's Kappa index: 0,77 [CI 95%: 0,633 - 0,906]) and 92% (95% CI: 0,86 - 0,959) for women home-collected flocked swabs (Cohen's Kappa index: 0,74 [CI 95%: 0,588 - 0,883]). Overall agreement between home self-collected and clinician-collected vaginal flocked swabs, both tested with HPV SelfyTM, was 96,4% (95% CI: 0,917 - 0,988), confirming that the vaginal home self-sampling procedure doesn't influence the HPV testing accuracy.

Conclusions: This clinical study proved a substantial agreement between home self-collected and clinician-collected vaginal flocked swabs in this referral population, proving that home self-sampling procedure was easy and, furthermore, the samples shipping didn't compromise the HPV detection. Accordingly, these results suggest that the home self-sampling LadyMed HPV TestTM (Ulisse BioMed) could be a valuable method to increase cervical cancer screening coverage in particular to the hard-to-reach women.

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FC 16 - Self-sampling (III)

#0365

10 - Self-sampling

URINARY HPV DNA TESTING AS A TOOL FOR CERVICAL CANCER SCREENING IN FRANCE: AN UPDATE OF THE CAPU3 STUDY

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Background/Objectives: In France, since July 2019, cervical cancer screening is based on HPV testing on cervical smear for women aged 30 to 65, and cytological examination of a Pap smear for women aged 25 to 29. But screening coverage is unsatisfactory. Previous studies in our lab have shown that urinary HPV testing for high-risk HPV (HR-HPV) testing increases rates of compliance (1, 2). Since November 2016, the CapU3 study aims to invite more than 13000 women aged 35 to 65 who did not performed a Pap smear since 2010 in Maine et Loire department (France). In collaboration with the Cancer screening coordination center of the Pays de la Loire region, we conducted a study to offer urinary HPV testing for women who don't have regular cervical smear in order to increase the screening coverage in our department.

Methods: 500 to 700 letters proposing an at-home urinary HPV testing are sent monthly. With the letter, the women receive an urinary HPV DNA testing information note, a letter of consent, a sterile container, a procedure protocol, a bubble envelope and a prepaid return envelope. Women accepting to participate send their first-stream urine samples by mail to the Virology Laboratory in accordance with a three-rule secure packaging protocol as recommended in France. HR-HPV detection is performed using a real-time PCR technique (Anyplex II HPV28 Detection, Seegene®) that detects 19 HR-HPV genotypes. Patients with HR-HPV positive results are encouraged to perform a cervical smear as soon as possible to detect the presence of cervical lesions. For HR-HPV negative women, a Pap smear within 1 year is recommended for those women who do not have regular gynecological follow-up.

Results: Between November 2016 and November 2018, 13535 letters were sent to women. After exclusion (past hysterectomy, recent smear or refusal), the participation rate is 15.4%. Out of the 1915 analyzed specimens, 1711 and 190 were negative and positive for at least 1 HR HPV respectively. HR-HPV others than HPV 16 or HPV 18 were mostly detected as HPV 53 (23.7%) and HPV 68 (14.2%). Invalid results occurred in only 14 samples (0.7%). Among the smears, 23 abnormal smears were observed and 6 high-grade cytological lesions after colposcopy and biopsy have been detected.

Conclusions: Because home HPV urinary testing is non-invasive and do not require medical attention, this method may be an alternative for women who are reluctant to use Pap smear. Furthermore, 89.5% of the HPV-positive women benefited from a Pap smear collected by a clinician during follow-up. So, the urinary HPV test could be an alternative to the usual screening by cervical smear thus extending screening coverage in our department.

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#0464

10 - Self-sampling

HPV SELF-SAMPLING AS A ROUTINE OFFER TO SCREENING NON-RESPONDERS IN THE CAPITAL REGION OF DENMARK.

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Background/Objectives: In Denmark all women 23 to 65 years of age are offered cytology-based screening in the cervical cancer screening program. Overall, 73 % of invited women participate, but participation is slowly declining. However, 45 % of all newly diagnosed cervical cancers are found among women not attending screening. To address this issue and increase the participation in cervical cancer screening program, the Capital Region of Denmark is currently inviting all non-attending women to a routine HPV self-sampling offer as an alternative to the regular screening offer.

Methods: Between December 2017 and end of 2018, 59,874 screening non-attending women were invited for HPV self-sampling in an Opt-In fashion. Invitations were distributed by regular mail. Opting-In was possible by letter, phone, E-mail or through a specially designed web-platform. Invitation reminders were mailed after 8 weeks. Women opting-in and receiving a HPV self-sampling kit were reminded after 8 weeks to return the brush for analysis. Returned self-sampling brushes were analyzed using the BD Onclarity HPV assay after resuspension into 3 ml cervical brush diluent. If HPV positive, women were recommended for general practitioner (GP) collected follow-up cytology sample. Women with negative HPV self-sampling were returned to the next regular screening interval.

Results: 27 % (15,962) of all invited women, opted-in for HPV self-sampling, and 62 % of these returned the brush for analysis (10,178 participants, 17 % overall). Reminders were sent to 78 % of the invited women. Around 60 % of the responding women used the special designed web plat form for ordering the HPV brush, 30% answered by letter and 10 % by Email/phone. The HPV prevalence in women accepting self-sampling was 16 %. Off these, 88 % have complied with the follow-up recommendation for a GP collected sample. As an added effect of the self-sampling participation, 11 % of the invited women underwent GP based cytology screening after receiving the invitation for the HPV self-sampling resulting in an overall intention to treat participation rate of 28 %.

Conclusions: Here we report the first large scale operational experience from the general roll-out of the HPV self-sampling to all non-attending women residing in the Capital region of Denmark. The HPV self-sampling was well-received by the Danish women with 28 % responding to the offer. The follow-up rate after a positive HPV self-sample was high. The purpose designed web-platform was the most often used method of replying and the reminders had a large effect on the participation rate, underling the importance of timely communication. In conclusion HPV self-sampling offer is a promising initiative to improve the participation in organized screening.

References: Additional contribution.

#0468

10 - Self-sampling

SELF-SAMPLING AMONG LONG-TERM NON-ATTENDERS TO CERVICAL CANCER SCREENING IN NORWAY: A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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Background/Objectives: Attendance to the Norwegian cervical cancer screening program is currently suboptimal at 67%. To achieve more efficient cervical cancer prevention, it is important to remove barriers to screening attendance. This study aims to develop knowledge as to whether vaginal self-sampling for human papillomavirus (HPV) testing may increase cervical cancer screening attendance among women who have not attended screening for at least 10 years in Norway.

Methods: A pragmatic randomized controlled trial on the effect of vaginal self-sampling on screening attendance was initiated in April 2019. 6000 Norwegian women aged 35-69 who had not attended screening for at least 10 years were targeted. The study participants were equally randomized to either receiving (i) a reminder to attend regular screening (control group), (ii) a self-sampling kit directly mailed (opt-out group), (iii) an offer to order a self-sampling kit by mail, e-mail, or webpage (opt-in-group). Women who returned a positive self-sample were scheduled for follow-up at their regular general practitioner or a gynecologist. The final invitations to the study were dispatched in August 2019.

Results: The trial is on-going, but preliminary results suggest that 11% of women who were offered to order a self-sampling kit returned a self-sample (opt-in group), while 22% of women who received a self-sampling kit directly returned a self-sample (opt-out group). So far, all women with a HPV positive self-sample have complied to follow up. The high-risk HPV positivity rate among the returned self-samples is currently 12%. We will present updated results at the conference.

Conclusions: Direct mailing of a self-sampling kit as well as offering to order a self-sampling kit increased attendance to cervical screening among long-term non-attending women. Compliance to follow-up was high. The results from this study will aid decisions regarding if and how self-sampling should be offered in the context of organized screening in Norway.

#0474

10 - Self-sampling

HPV PREVALENCE AND GENOTYPING FREQUENCIES IN SCREENING NON-ATTENDERS ACCEPTING HPV SELF-SAMPLING

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Background/Objectives: In Denmark all women between the age of 23 and 65 are offered cytology-based screening in the organized cervical cancer screening program. However, 27% of the invited women does not participate. In 2017 the Capital Region of Denmark started a large-scale initiative offering all screening non-attending women HPV self-sampling. Denmark has a high background prevalence of HPV in women ≥30 years attending cervical cancer screening (11.3%) with HPV16 being the most prevalent genotype. Here we present HPV prevalence and genotyping frequencies in screening non-attending women accepting HPV self-sampling.

Methods: Between December 2017 and end of 2018 59,874 screening non-attending women (age 27-69) have been offered an HPV home test. 17 % (10,178) of the women sent the HPV home test back for analysis. The Evalyn dry brush from Rovers was used in the initiative, and upon arrival in the laboratory the brush head was resuspended in 3 ml BD CBD medium and 1 ml was used for BD Onclarity HPV testing according to the manufacturer's recommendations. The Onclarity assay is a real time PCR HPV assay, detecting 6 genotypes individually (18, 16, 31, 45, 51, 52) and eight genotypes in three bulks (33/58, 35/39/68, 56/59/66). A population of 991 (≥30) women attending the ordinary screening program tested with the Onclarity assay was used for reference.

Results: The overall oncogenic HPV positivity of self-sampling was 15.5% amongst 10,178 analyzed self-samples. HPV prevalence was 18.1 % in women age 27-29, 19.3 % in women age 30-39, 12.9 % for women 40-49 and 11.9 % for women 50-59, and 10.8 % for women age 60-69. Overall prevalence was 14.3 % in women 30 years or above. The most prevalent genotype was HPV 16 with 2.9 %, followed by 31, 51, 52, 45, and HPV18. The three bulks reported by the Onclarity assay showed a prevalence of 2.0 % (33/58), 3.9 % (56/59/66) and 3.9 % (35/39/68). For comparison, HPV prevalence by Onclarity was 11.3 % in 991 women 30 years or above attending the ordinary cervical screening program, with HPV16 with the highest prevalence. All self-sampling positive women are referred to a doctor collected follow-up sample within 3 months of the positive self-sample. At present 88% of all HPV self-sampling positive women have followed that recommendation.

Conclusions: The HPV prevalence in non-attending women accepting HPV self-sampling was slightly higher compared to women attending the ordinary screening program. HPV16 had the highest prevalence in both women accepting self-sampling and women with cytology-based screening. In conclusions, HPV self-sampling combined with a strategy of referral to a follow-up doctor collected cytology sample acts to shuttle the women in question into the regular national screening algorithms. Therefore, this combination of self-sampling and follow-up represents a robust HPV testing of women not attending cervical cancer screening which by the HPV prevalence observed is indeed a much needed alternative to the current cytology based screening.

#0672

10 - Self-sampling

Feasibility and Triage Study of HPV Genotyping of Self-Sampling Cervical Cancer Screening on Internet-Based in China

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Background/Objectives: In order to improve the coverage population of cervical cancer screening, it is necessary to establish a mode with self-sampling cervical cancer screening-management on Internet-based in China. We extend and conduct this mode to different regions and different groups of Chinese women.

Methods: Totally 10,056 women aged 30~59 years with self-sampling were recruited for cervical cancer screening between September 2018 and May 2019 in 8 provinces and autonomous regions in China, and 984 had histological diagnosis within one month after HPV testing. The 21-genotyping HPV testing was performed by BMRT real time PCR assay (Jiangsu BioPerfectus Technology, Taizhou, China),which genotypes 13 hrHPV, 5 potential hrHPV and 3 low-risk HPV separately. The website of cervical cancer screening (http://47.106.227.241/) was designed. Women registered online with personnel information, signed online informed consent form and screened systematically eligible subjects. After an application was approved and obtained a QR code for received self-sampling brushes, went home or on-site for self-collected samples by women themselves from the vagina, and send back samples finally. HPV testing results would feedback online and provide medical care suggestion. This is called internet-based self-sampling cervical cancer screening mode. The feeling and acceptability of self-sampling were investigated after sampling.

Results: Of the 10,056 attenders, The rate of success of self-sampling was 99.86% (10042/10056).HPV infection rate is 15.56%(1565/10,056) among 8 provinces in China. The highest and lowest HPV positive rate is 21.75% in Inner Mongolia, and 8.89% in Guangdong, separately(Figure 1). The positive proportion of the top 5 HPV genotypes were HPV52, -16, -58, -39 , -56(Figure 2). However, of the 14 hrHPV involving HSIL+ cases, HPV16, -33, -52, -58 were most likely to develop HSIL+ , and HPV45, -51, -66 were the 3 least genotypes (Figure 3). In addition, women were asked questions related to the acceptability of self-sampling and HPV testing, like " Do you feel that the self-sampling method is easy or difficult to master? ", " Do you use the self-sampling brush to collected sample for discomfort or comfortable ? ", and " When you are screening for cervical cancer with HPV testing, you are more likely to choose self-collected sampling or clinician-collected sampling? ". 92.3% women feel it is easy to master self-sampling, 86.4% have no discomfort when using self-sampling brush, and 60.8% attenders are more likely to choose self-sampling for cervical cancer in the future.

Conclusions: Extensive genotyping could identify some more high-risk genotypes for detecting HSIL+, apart from HPV 16/18,HPV33, HPV31, and HPV52 might be 3 potential hrHPV genotypes in China, showed a higher prevalence in detection of HSIL+ lesions, may be as a triage way. The percentage of the acceptability of self-sampling is higher, the self-sampling cervical cancer screening on internet-based is a simple, convenient and very promising cervical cancer screening model in the future in China.

Figure 1 HPV prevalence in eight provinces from China

#0513

10 - Self-sampling

HIGH RISK HPV STATUS IN FIRST VOID URINE COLLIPEE SAMPLES VERSUS PHYSICIAN-COLLECTED CERVICAL SPECIMENS DETERMINED BY A PCR-BASED CLINICALLY VALIDATED SCREENING TEST

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Background/Objectives: Urine has been suggested to be a useful alternative sample type to test for the presence of high risk HPV (hrHPV) DNA in cervical cancer screening. Urine sampling for laboratory diagnostics is a well-established non-invasive procedure and is expected to be less associated with barriers compared to physician-sampling of cervical scrapes. Objective Within the VALHUDES framework, this study aims is to investigate whether hrHPV DNA testing on first-void urine with a PCR-based assay validated for use in primary cervical cancer screening can detect hrHPV DNA at clinically relevant levels by comparison to physician-collected samples.

Methods: Matched pairs of urine (ColliPee; Novosanis, Wijnegem, Belgium) and physician-sampled cervical scrapes (Cervix Brush Combi; Rovers, Oss, The Netherlands) in PreservCyt liquid-based cytology (LBC) medium from 402 women (25-64 years of age) referred for colposcopy between January 2018 and August 2019 were tested side-by-side with the RealTime High Risk HPV assay (Abbott GmbH, Wiesbaden, Germany) on the m2000 System. Samples were collected at home prior to their visit to one of the participating colposcopy centres. HrHPV DNA detection rate per sample type and concordance of hrHPV results observed with both sample types were calculated. Urine samples were considered to be hrHPV positive if any PCR cycle number (CN) was reported, while hrHPV results from reference samples reported by the assay software were used for comparison.

Results: The overall hrHPV DNA detection rate in first-void urine samples was 65.4% versus 56.7% in matched physician-collected cervical LBC samples. The overall agreement of hrHPV DNA results on both sample types was 83.3% with a kappa value of 0,65 (95%CI: 0.58 - 0.73). Considering the physician-collected sample as reference, the sensitivity of the swab was 93.0% (95%CI: 89.7% - 96.3%) and the specificity 70.7% (95%CI: 63.9% - 77.5%). This renders a false positive rate of 29.3%, and false negative rate of 7.0%. Considering "HPV16', "HPV18' and "Other HR-HPV' separately, the agreement was 95.8%, 98.3%, and 82.1% respectively. Respective Kappa values were 0.81, 0.84, and 0.64.

Conclusions: Our results indicate a higher overall hrHPV DNA detection rate in first-void urine collected with Colli-Pee and a "good' concordance with matching physician-sampled cervical LBC samples. For HPV16 and HPV18 "excellent' concordance was observed. Future analyses of hrHPV results taking histological status patient status into account are expected to provide further insight into the potential of hrHPV DNA testing on first-void urine (Colli-Pee) for the prediction of cervical disease.

#0704

13 - Screening for women difficult to reach

A new self collection Quick Brush device for primary smear and HPV test, designed on the same principle that periodic tampon with applicator (medium size). Comparison results for morphological changes and HPV testing.

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Background/Objectives: Cervical cancer is cause by HPV in almost 100% of cases. Screening policies vary widely from one country to another (primary smear + HPV test in the case of morphological changes, primary HPV testing or mixed solution. In France, there was also a very large variation in screening by region, from 41.6% to 72.5%. Nearly 60% of non-participants in screening were in a city identified as disadvantaged associated with the difficulty to obtain an appointment with gynecologists. As part of the improvement of cervical cancer screening, the development of an original method of self-collection, similar to hygienic tampon with applicator, identical in all respects to that performed by the gynecologist in his office, seemed particularly interesting.

Methods: The new Quick Brush device consists of a sampler brush device and its applicator designed on the same principle that periodic tampon with applicator (medium size). The applicator consists of an outer tube containing the sampler device and an inner tube (pusher). The material used is medical grade low density polyethylene, with at the top 71 strands cervico-vaginal sampling brushes. These 71 strands constitute a circular brush that multiplies the sampling surface and statistically reproduce the manual gesture usually performed by the practitioner under speculum. Brush contact is 20 seconds before introduces (60 seconds) the brush into liquid medium Surepath BD for transport and transport/conservation, shaking gently, before discarding it. The Quick Brush device was proposed to all patients receiving a screening smear at gynecologist office to benefit from a double smear, the first performed by the patient herself (self- sampling), the second, during the same consultation, by Dr. Thierry Haag who explained the entire procedure in detail to the patient. The same patient was taken in the traditional way (smear with brush + speculum).

Results: In total, the study involved 27 women aged 20 to 72 years (mean 45.5 ± 13.5 years). Three were under 30 years of age (11.1%), 8 were 30 to 39 years old (29.6%), 6 were 40 to 49 years old (22.2%), 7 were 50 to 59 years old (25 years old). 9%), and 3 years of age 60 or older (11.1%) The delay between harvesting was 13 to 19 days (mean 16.1 ± 3.0). Among the samples taken by the doctor, 2 were considered insufficient to allow anapath examination (7.4%), against none in self-samples (paired chi2 = 2.00, p = 0.16). The 2 samples were taken one from a 68-year-old woman; the other, 36 years old. In addition, a smear was considered ASCUS for self-sampling and normal for medical sampling.

Conclusions: All the samples were judged to be of sufficient quality. The auto collection kit largely eliminates the pain. The result of this study is very positive and improve the practice of HPV screening. The QUICK BRUSH Kit could be used for systematic mass screening campaigns of the HPV and be distributed through drugstore/pharmacy, to general practitioners (no constraint of a speculum examination) and for patients with significant vaginal atrophy. This self-collection will ultimately be particularly useful for women who do not participate in the first screening.

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FC 17 - Molecular markers (I)

#0345

12 - Molecular markers

CERVICAL CANCER SCREENING IN VACCINATED WOMEN: WILL P16/KI67 DUAL STAINING BE AN OPTION FOR TRIAGING HPV POSITIVE WOMEN IN A POPULATION WITHOUT HPV 16 OR HPV 18 INFECTION?

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Background/Objectives: It is important to define the best screening methods for girls vaccinated against HPV. In Italy, the women offered HPV vaccination in 2007/08 have started to access cervical cancer screening in 2017. We evaluate the performance of p16/ki67 dual staining as triage test according to HPV genotyping in a screening population within the NTCC2 (New Technologies in Cervical Cancer 2) trial. To simulate the performance of the test in vaccinated women, we considered high risk HPV-no16/18-positive women (HR-other) as a proxy for vaccinated.

Methods: Women were recruited in 3 centres. HPV (Cobas 4800 assay) positive women were triaged with cytology and tested for p16/ki67. Women with positive cytology were referred to colposcopy; those negative were randomised to immediate colposcopy or to 1-year HPV re-testing. In women with HPV16 and/or 18 vs HR-other infection, we compared the performance of p16/ki67 as triage test in terms of CIN2+ sensitivity, 1-year HPV persistence in p16/ki67-negative, immediate colposcopy referral and PPV. All the CIN2+ found within 24 months since recruitment are included.

Results: 23.672 women were recruited; 1446 (6.1%) were HPV positive. p16/Ki67 dual staining was valid in 1297 women, 345 with HPV16/18 and 952 with HR-other. Cumulatively, 52 CIN2+ were found, 32 in HPV16/18 and 20 in HR-other infections. Sensitivity was 93.3% and 70.6%, immediate referral was 40.9% and 24.1%, PPV would be 23% and 7%, 1-year HPV persistence in p16/ki67-negative was 70.8% and 52.8% in HPV16/18 and HR-other respectively. Table : Performance of p16/ki67 dual staining as triage test in women with HPV 16 and/or 18 and other high risk type infections Women CIN2+ Prevalence ‰ Sensitivity % Immediate Referral % PPV % 1-year HPV persistence % All HPV-pos 1297 52 4.0 (3.0-5.2) 85.1 (71.7-93.8) 28.7 (26.1-31.3) 13.2 (9.5-17.4) 56.8 (51.2-62.3) HPV 16/18 pos 345 32 9.3 (6.4-12.8) 93.3 (77.9-99.2) 40.9 (35.5-46.4) 23.0 (15.7-31.5) 70.8 (58.9-81.0) HR-other pos 952 20 2.1 (1.3-3.2) 70.6 (44.0-89.7) 24.1 (21.3-27.1) 7.0 (3.8-11.6) 52.8 (46.4-59.1)

Conclusions: In women with HR-other, both sensitivity and PPV of p16/ki67 are lower than in women with HPV16/18. In a screening program for vaccinated women, where the majority of HPV infections will be by HR-other types, performance of the triage test will worsen. The use of HPV tests with genotyping could allow selective assessment according to risk, allowing less intensive protocol and longer intervals for other-HR infections.

#0487

12 - Molecular markers

First results from the VALHUDES study: use of first-void urine for cervical cancer screening.

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Background/Objectives: The use of first-void urine - i.e. initial stream of urine - as liquid biopsy to collect biomarker containing cervicovaginal secretions has proven to be promising for cervical cancer prevention. Despite that good HPV DNA agreements between paired first-void urine and cervical samples have been reported, few clinical accuracy data of high-risk (hr)HPV testing on first-void urine are available. Which have been found to vary substantially by study , setting and applied procedures. To investigate this knowledge gap, the VALHUDES (Validation of Human Papillomavirus Assays and Collection Devices for Self-samples and Urine Samples) protocol was designed as a diagnostic test accuracy study that aims to compare the clinical sensitivity and specificity of particular hrHPV assay(s) on self-samples, including first-void urine, collected in agreement with standardized protocols and hrHPV testing on matched clinician-taken samples.

Methods: Paired first-void urine (home-collected), self-collected vaginal (collected at the clinic), and clinical-collected cervical samples are collected at five colposcopy centres including a total of 500 women (25-64 years) that are referred to colposcopy due to cytological abnormalities (NCT03064087, Arbyn J Clin Virol 2018). Sample sets are subsequently analysed in a laboratory accredited for HPV testing. The following assays are foreseen to be evaluated in first-void urine: RealTime High Risk HPV assay (Abbott), cobas-4800 and -6800 (Roche), Onclarity (BD) and Riatol qPCR HPV genotyping assay. Disease verification for all enrolled patients is provided by colposcopy combined with histological assessment of biopsies. Preliminary HPV results are obtained already for the Abbott RealTime HighRisk HPV assay. Impact of freezing was also evaluated in 26 first-void urine samples.

Results: To date, 420 out of 500 paired first-void urine, vaginal self-samples, and clinician-collected cervical samples were successfully included. First urinary results from at least 100 women using the Riatol qPCR HPV genotyping assay and cervical data as reference will be presented at the conference. HPV test results on first-void urine samples frozen at -35°C and -80°C was non-inferior to fresh collected samples; stored between 2-8°C upon arrival at the lab and analysed within seven days post collection.

Conclusions: The execution of the VALHUDES protocol runs smoothly and first preliminary urinary HPV results are promising. The application of first-void urine for primary HPV testing in clinical practice was also strengthened by the fact that a freeze thaw cycle doesn't affect the HPV test results, which allows laboratory staff to store and run the samples in batch.

#0711

11 - Genotyping

VALIDATION OF TARGETED NEXT GENERATION SEQUENCING PANEL FOR HPV-GENOTYPING IN CERVICAL CANCER

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Background/Objectives: Background: The vast majority of all cervical cancer cases are caused by a persistent infection with the oncogenic virus HPV, and previous studies have shown that if HPV is integrated into the DNA of the cervical host cells, there is an increased risk for these women to develop cervical cancer. Objectives: To develop a sensitive method based on targeted Next Generation Sequencing (NGS) for early and precise detection of specific high-risk HPV-genotypes that is highly associated with the development of cervical cancer, and to investigate the viral integration status of the cervical lesions.

Methods: The study was conducted on a cohort of 108 women between 28 and 83 years old. The cohort was divided into groups: Cervical cancer (n=78), CIN2 lesions progressed to CIN3 or cervical cancer (n=5), CIN2 cleared lesions that did not progress (n=5), a normal control group (n=10), and baseline blood samples from cervical cancer patients (n=10). In this study, the IonTorrent NGS technology was applied, and a targeted NGS panel was designed to detect a total of 25 high-risk and probably high-risk and 2 low-risk HPV genotypes in DNA and RNA, as well as to investigate the viral integration status of the cervical lesions. The NGS panel was applied to FFPE (formalin-fixed paraffin-embedded) cervical biopsies as well as on blood samples to further determine the sensitivity of the method. The method was validated with SPF10 LiPA 25 HPV test as well as an already validated qPCR assay.

Results: It was possible to detect the following HPV genotypes: HPV-16, 18, 31, 33, 35, 45, 51, 58, 59 in the samples with a high signal-to-noise ratio. The results showed a high agreement with data assessed by SPF10 LiPA 25 HPV test. Integrated HPV was detected in CIN2, CIN3, and cervical cancer samples and these finding were validated by a qPCR assay. HPV was not detected in the CIN2 cleared group, whereas in CIN2 from the progressed group the same HPV type in the corresponding CIN3 or cancer sample was detected in 80% (4/5) of the cases. HPV detection and genotyping of baseline blood samples showed full agreement with ddPCR assessment of HPV-positive as well as negative blood samples.

Conclusions: This proof of concept study has shown that it is possible with great objectivity to detect and genotyping different HPV types utilizing a targeted NGS panel, both in FFPE and blood samples. This method provides for early diagnosis and prognosis of disease progression in preneoplastic lesions and in cervical cancer samples as well, thereby optimizing the potential of recovery and survival for these patients. The NGS method provides a high throughput, easily adapted to a modern molecular laboratory, and is highly cost-effective. Furthermore, it is known that several other cancer types such as head and neck cancer and cancers of the anogenital region also are associated with high-risk HPV infection, and it is therefore suggested that this method can be utilized for early diagnosis of these cancer types as well.

#0369

20 - New technologies

PERFORMANCE OF COMBINATIONS OF BIOMARKERS AS TRIAGE FOR HPV-DNA POSITIVE WOMEN IN CERVICAL CANCER SCREENING

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Background/Objectives: The New Technologies for Cervical Cancer 2 (NTCC2) trial aimed at evaluating E6/E7 mRNA overexpression and p16/ki67 dual staining for their performance in triaging HPV DNA positive women within organized cervical cancer screening. The present analysis compares the performance of seven different combinations of tests (i.e., cytology, E6/E7 mRNA overexpression, p16/ki67, and HPV 16-18 typing) as triage strategies for HPV-DNA positive women.

Methods: Women were recruited in four centres within organised screening and tested with HPV DNA Cobas 4800 or Hybrid Capture 2 assays. HPV DNA positive women were triaged with cytology and tested for E6/E7 mRNA and p16/ki67. Women with abnormal cytology were referred to colposcopy; those negative were randomised to immediate colposcopy or 1-year HPV re-testing. Here we present the immediate colposcopy referral and CIN2+ sensitivity, with 95% Confidence Interval (95%CI), of cytology at ASCUS+ and high grade (HG) thresholds, E6/E7 mRNA overexpression, p16/ki67 (including not evaluable cases among positive), and HPV 16-18 typing for women tested with Cobas 4800, alone or in combination. To be considered as positive, combinations with "AND" required the positivity of both tests, combinations with "OR" the positivity for one of the two. All lesions found within twelve months of follow-up are included.

Results: 40509 women were recruited; 3147 (7.8%) were HPV-DNA positive (1446 tested with Cobas). Cumulatively, 174 CIN2+ were found (52 among women tested with Cobas). Cytology referred to immediate colposcopy 26.5% of tested women at ASCUS+, and 5.9% at HG threshold; sensitivity was 66.1% (95%CI 58.5-73.1) and 47.1% (95%CI 39.5-54.8), respectively. E6/E7 mRNA overexpression showed the highest immediate referral (66.8%) and sensitivity (96.0%; 95%CI 91.9-98.4). p16/ki67 tested positive in 32.1% of women, with a sensitivity of 78.7% (95%CI 71.9-84.6). The immediate referral with HPV 16-18 typing was 27.0%, with a sensitivity of 61.5% (95%CI 47.0-74.7). The performance of combinations of tests for triage of HPV-DNA positive women are reported in Table 1.

Conclusions: The combination of HPV 16-18 typing with cytology or with p16/ki67 resulted in high sensitivity, but with a substantial increase in colposcopy referral compared to single test strategies.

References: *The following are components of the New Technologies for Cervical Cancer 2 Working Group: Regione Lazio: Alessandra Barca, Francesco Quadrino. IRCCS Regina Elena National Cancer Institute, Rome: Maria Benevolo, Francesca Rollo. AUSL Reggio Emilia: Paolo Giorgi Rossi, Pamela Mancuso, Francesco Venturelli, Gabriele Carlinfante, Teresa Rubino. ISPRO Florence: Francesca Maria Carozzi, Simonetta Bisanzi, Massimo Confortini, Carmelina Di Pierro, Giulia Fantacci, Anna Iossa, Alessandra Mongia, Cristina Sani GiamPaolo Pompeo, Donella Puliti, Andrea Baldini . CPO and Centro Unico di Screening Cerv Vag, Turin: Guglielmo Ronco, Raffaella Rizzolo, Anna Gillio Tos, Laura De Marco, Elena Allia. APSS, Trento: Teresa Pusiol, Mattia Barbareschi, Emma Bragantini. USL Umbria1, Perugia: Basilio Passamonti, Daniela Gustinucci, Simonetta Bulletti, Elena Cesarini, Maria Donata Giaimo. Este Monselice (PD): Gabriella Penon, Alessandra Bertazzo, Laura Toniolo, Angelo Farruggio, Natalina Marchi; Istituto Oncologico Veneto IOV-IRCCS: Annarosa Del Mistro, Helena Frayle, Silvia Gori; Registro Tumori del Veneto: Manuel Zorzi; UOC Screening e VIS: Elena Narne, Anna Turrin.

Table 1. Performance of combinations of tests for triage of HPV-DNA positive women

#0372

12 - Molecular markers

INTEROBSERVER REPRODUCIBILITY OF P16INK4A/KI67 DUAL STAINING IN HPV POSITIVE WOMEN IN THE SCREENING POPULATION FROM THE NTCC2 STUDY

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Background/Objectives: The dual-staining for p16 and ki67 proteins, is one of the most promising biomarker as triage test of HPV-DNA positivity. Although it has been largely validated, limited data has been published on the reproducibility of its interpretation, taking into account mainly positivity agreement. In this study we assessed the inter-laboratory reproducibility of the test interpretation, considering both adequacy and positivity agreements, in an unselected screening HPV-positive population enrolled within the Italian NTCC2 study.

Methods: Liquid based cytology slides from HPV-DNA positive women, were immunostained for p16/ki67 in 4 Labs and were interpreted in 7 Labs. The slides circulated among Labs, since every slide had 3 reports from 3 different Labs. Results were classified as positive (at least one double stained cell), negative, or inadequate. Inter-laboratory reproducibility was evaluated for the overall agreement by kappa values for multiple raters and the relative ninety-five percent confidence intervals (95%CI), using the bootstrap method with bias correction.

Results: Overall, we obtained 9300 reports from 3100 cases. 905 reports were inadequate (9.7%). The overall concordance for adequacy was poor (multiple-rater-K=0.224, 95%CI: 0.183-0.263). Taking into account only the evaluable reports, the overall concordance for positivity was moderate (K=0.583, 95%CI 0.556-0.610). Of the 176 CIN2+ lesions found in HPV-DNA positive women, 158 had a valid p16 result: 107 were positive by all 3 reports (sensitivity for CIN2+: 67.7%, 95%CI: 59.8%-74.9%), 23 by two (sensitivity of majority report: 82.3%, 95%CI: 75.4%-87.9%) and 15 by one report (sensitivity of at least one positive result: 91.8%, 95%CI: 86.3%-95.5%). 13 CIN2+ cases were negative by all the 3 reports. The overall concordance for positivity in CIN2+ samples was K=0.487 (95%CI: 0.429-0.534), while in the non-CIN2+ samples was K=0.558 (95%CI: 0.528-0.588).

Conclusions: The p16/ki67 assay showed a poor reproducibility for adequacy and a good one for positivity, comparable to that of cervical cytology. Nevertheless, the low reproducibility does not impact on sensitivity for CIN2+. Further investigations on accuracy indicators are needed to best understand the possible role of this biomarker as triage test of HPV positivity in real clinical practice.

References: *The following are components of the New Technologies for Cervical Cancer 2 Working Group: Regione Lazio: Alessandra Barca, Francesco Quadrino. IRCCS Regina Elena National Cancer Institute, Rome: Maria Benevolo, Francesca Rollo. AUSL Reggio Emilia: Paolo Giorgi Rossi, Pamela Mancuso, Francesco Venturelli, Gabriele Carlinfante, Teresa Rubino. ISPRO Florence: Francesca Maria Carozzi, Simonetta Bisanzi, Massimo Confortini, Carmelina Di Pierro, Giulia Fantacci, Anna Iossa, Karin Louise Andersson, Alessandra Mongia, GiamPaolo Pompeo, Cristina Sani, Donella Puliti, Andrea Baldini. CPO and Centro Unico di Screening Cerv Vag, Turin: Guglielmo Ronco, Raffaella Rizzolo, Anna Gillio Tos, Laura De Marco, Elena Allia. APSS, Trento: Teresa Pusiol, Mattia Barbareschi, Emma Bragantini. USL Umbria1, Perugia: Basilio Passamonti, Daniela Gustinucci, Simonetta Bulletti, Elena Cesarini, Maria Donata Giaimo. ULSS17 Este Monselice: Gabriella Penon, Natalina Marchi, Angelo Farruggio, Alessandra Bertazzo, Laura Toniolo. Istituto Oncologico Veneto-IOV-IRCCS: Annarosa Del Mistro, Helena Frayle, Silvia Gori; Registro Tumori del Veneto: Manuel Zorzi. UOC Screening and VIS: Elena Narne, Anna Turrin

#0214

12 - Molecular markers

USE OF P16/KI67 FOR TRIAGE OF CERVICAL INTRAEPITHELIAL NEOPLASIA II-III IN PATIENTS INFECTED WITH HIGH RISK TYPE OF HUMAN PAPILLOMA VIRUS (HPV)

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Background/Objectives: Adding P16/Ki-67 Dual-immunostaining to HPV screening test has been shown to increase detection rate of high-grade cervical intraepithelial neoplasia (CIN2+). This study was aimed to evaluate the diagnostic performance of P16/Ki67 dual-staining, combined with co-testing (PAP/HPV), for the detection of histologic confirmed CIN2+.

Methods: Women aged 20-70 years coming for liquid-based cytology (Surepath®, BD Diagnostics, Burlington, NC, USA) combined with Cobas® 4800 HPV DNA Testing (Roche, Pleasanton, CA, USA) and having positive HPV were invited to participate in the study. Study was conducted between August 2017 to July 2019 (N=205) at Chulabhorn Hospital, Bangkok, Thailand. P16/Ki67 testing (CINtec® PLUS Cytology by Roche mtm laboratories, Mannheim, Germany) was performed on residual cytologic material within 6 months after specimen collection. Colposcopy and colposcopic directed biopsy were done in all patients. Pathologic results were correlated to positive or negative P16/Ki-67 test.

Results: Sensitivity of P16/Ki-67 dual-staining for the detection of CIN 2+ in women infected with either HPV 16/18 or other high-risk genotypes was 78.8% (26/33 cases). Specificity and positive predictive value (PPV) were 62.8% (108/172 cases) and 28.9% (26/90 cases), respectively. Overall accuracy of P16/Ki67 test was 65.4%. Negative predictive value (NPV) was high at 94.0% (108/115 cases). Combining dual-staining with PAP smear, negative predictive value for the detection of CIN 2+ in negative cytology was 95.0%, ASC-US was 88.9% and LSIL was 96.0%.

Conclusions: P16/Ki-67 dual-stained cytology combined with co-testing represents a high negative predictive value and potentially be used to avoid unnecessary colposcopy in patients with negative and low-grade cytology.

#0151

12 - Molecular markers

MOLECULAR PROFILING AS A TRIAGE FOR hrHPV POSITIVE WOMEN

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Background/Objectives: Nearly all cervical cancers are associated with high-risk human papillomavirus (hrHPV) infections. Therefore detecting hrHPV presence is becoming a primary screening tool in nation-wide cervical cancer screening programs. HrHPV testing is highly sensitive but cannot distinguish transient from persisting infections, resulting in unnecessary referrals, overtreatment and prolonged follow-up. Moreover, it is still not known why some women infected with hrHPV will clear the infections, and others will not. We postulate that we can stratify the risk for development of cervical cancer by profiling hrHPV transcriptional activity, together with host transcriptome.

Methods: We applied targeted RNA next generation sequencing (t/RNA-NGS) to profile cancer-related host transcripts as well as viral transcriptome in cervical tissues (both scrapes and biopsies) using single molecule molecular inversion probes (smMIPs).

Results: We developed a new targeted sequencing approach (t/RNA-NGS), in which we can profile hrHPV transcriptional activity, together with host transcriptome in one assay, on hundreds of cervical samples simultaneously. To validate this comprehensive approach, we first assessed if we could use our test to genotype hrHPV on RNA level. RNA-based genotyping of hrHPV subtypes, without prior knowledge of HPV status, was concordant with the DNA-based genotyping. Next we used a small cohort of cervical cancer biopsies (n=18) and controls (n=4) to validate whether we can profile the transcriptional activity of hrHPVs. We were also able to profile the transcriptional activity of detected hrHPV subtypes by measuring viral E2, E6 and E7 gene expression levels. To discover cervical cancer biomarkers other than hrHPV, we performed agglomerative unsupervised cluster analysis of measured gene expression data excluding hrHPVs. Normal cervical tissues and cancer tissues clustered in two separate groups, identifying genes that are differentially expressed between those two groups. We are now profiling hrHPV transcriptional activity, together with host transcriptome in a big cohort of 380 random cervical scrape samples, to be able to validate whether we can better stratify the risk for development of cervical cancer.

Conclusions: Here we show that t/RNA-NGS is a powerful technique to obtain simultaneous information on hrHPV genotypes and hrHPV viral gene expression, as well as expression of other cancer-associated genes. It is an important advantage to profile host and viral transcriptome in one single assay. Future studies may confirm whether t/RNA-NGS has potential as a triage method for risk assessment and progression prediction in hrHPV-positive women.

#0075

12 - Molecular markers

HPV DNA IN THE BLOOD OF CERVICAL CANCER PATIENTS - CLINICAL IMPLICATIONS?

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Background/Objectives: Human papillomavirus (HPV) is the leading cause of cervical cancer. DNA from cancer tissue is released and circulate in the blood of cancer patients. In this study, we hypothesize that HPV DNA is released into the bloodstream from cervical tumour cells, and that these fragments of HPV DNA shed by tumour can be measured in blood samples from cervical cancer patients, making it a molecular marker useful for screening, prognosis and clinical monitoring of these patients.

Methods: From June 2018 to December 2020, blood samples from women newly diagnosed with cervical cancer at Aarhus or Odense University Hospital are collected. HPV testing and genotyping is performed on cervical tissue samples from all included women. A baseline blood sample taken prior to treatment initiation and follow-up blood samples taken during and after treatment are collected up until two years after termination of treatment. The study uses digital droplet PCR (ddPCR), a method based on dilution and partitioning of the blood sample in many reaction chambers or droplets, to measure absolute quantities of HPV DNA fragments in these blood samples.

Results: The study is ongoing, but preliminary results on blood samples from ten patients with HPV 16 positive cervical cancer have already supported our hypothesis that HPV DNA can be measured in the blood. Four of these patients were diagnosed with low-stage disease and six with disseminated high-stage disease. Our analyses showed that HPV 16 DNA was qualitatively and quantitatively measureable in blood samples from five of the six high-stage patients. The analyses on follow-up blood samples from these patients furthermore showed that HPV DNA quantity decreased concurrently with cancer treatment. In the blood of patients with low-stage disease, HPV 16 DNA was not detectable.

Conclusions: This study has established that HPV DNA can be qualitatively and quantitatively measured in blood samples of high-stage cervical cancer patients. Our preliminary results suggest that the viral load of HPV DNA in blood from cervical cancer patients correlates to the stage of the disease. If the coming results continue to show that HPV DNA is only measureable in patients with high-stage disease, this biomarker may be used as a predictive marker for disease stage at the time of diagnosis. In patients experiencing a recurrence of their disease, we expect to see an increase in the viral load of HPV DNA prior to this. If our coming results support this, we may have found a method to detect disease recurrences earlier than today, enabling us to initiate re-treatment in time. Since HPV is known to also cause other types of cancer, we expect the method to also be applicable in these diseases.

#0597

3 - Pathogenesis

MEK/ERK Signaling is a Critical Regulator of High-Risk Human Papillomavirus Oncogene Expression Revealing Therapeutic Targets for HPV-Induced Tumors

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Background/Objectives: Human papillomaviruses (HPVs) predominantly cause benign hyperplasia in stratifying epithelial tissues. However, a subset of carcinogenic or "high-risk" HPV (hr-HPV) genotypes are etiologically linked to nearly 5% of all human cancers. Hr-HPV-induced malignancies are driven by deregulated expression of the E6 and E7 oncogenes and the functions of these viral oncoproteins have been widely studied. Yet, the mechanisms that regulate hr-HPV oncogene transcription and suppress their expression in benign lesions remain poorly understood.

Methods: We used five independent human keratinocyte cell lines that maintain HPV16, HPV18 or HPV31 genomes episomally to investigate the cellular signaling pathways that are important for controlling HPV oncogene expression during proliferation and epithelial differentiation. HPV-positive cancer-derived cell lines with integrated viral genomes were also tested in culture and as tumor xenografts. Monolayer cell cultures, epithelial organotypic (raft) tissue models and neoplastic tissue biopsy materials were subject to our cellular, biochemical and genetic analyses. We tested the responses of these cells and tissue to signaling activation and suppression using immunoblot analyses for signaling activation and viral oncoprotein expression. RT-qPCR and in situhybridization studies were used to monitor viral oncogene transcription. Immunohistochemical staining revealed the correlations among cell signaling and viral oncogene and oncoprotein expression in experimental organotypic epithelial tissues and in tissue microarrays (TMAs) as previously described[1].

Results: We find that MEK/ERK signaling increases concomitantly with increasing neoplastic grade in human cervical intraepithelial neoplasia (CIN) lesions (specimens from 250patients with CIN and 330normal epithelium tissues; $X2= 212.7$, $p < 0.001$). The experimental models allowed us to determine how signaling influences HPV E6 and E7 transcription under proliferating conditions and when cells are subject to the physiologically relevant environments of two- and three-dimensional contact inhibition and epithelial differentiation. We demonstrate that EGFR/MEK/ERK signaling is a key regulator of hr-HPV oncogene expression at the transcriptional level. Stimulation of EGFR with a variety of ligands induces oncogene transcription in proliferating and contact inhibited contexts. We show that MEK/ERK signaling is normally suppressed by epithelial contact inhibition and differentiation cues, and thereby, regulates hr-HPV oncogene expression. Mechanistic studies show that pharmacological inhibitors of EGFR, MEK and ERK signaling quash HPV oncogene expression and the neoplastic phenotype in HPV-positive cells with both episomal and integrated genomes.

Conclusions: Our data suggest that HPVs are adapted to use the MEK/ERK signaling pathway to regulate their productive replicative cycles in benign lesions. Previous studies show that epidemiologically identified cancer promoting cofactors with hr-HPV infections [2]also promote MEK/ERK signaling [3-9]. This suggests a potentially shared mechanism by which these factors promote hr-HPV persistence and/or disease. As pharmacological inhibition of ERK signaling suppresses HPV E6 and E7 expression and the neoplastic phenotype, we propose this as a potential clinical strategy to suppress uncontrolled cell proliferation, reduce oncogene expression and treat HPV neoplasia.

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FC 18 - Anal neoplasia

#0229

27 - Anal neoplasia

THE UTILITY OF DIGITAL ANAL RECTAL EXAMINATIONS (DARE) IN A PUBLIC HEALTH SCREENING PROGRAM FOR ANAL CANCER

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Background/Objectives: There are no uniform screening recommendations for anal cancer. Medical practice guidelines are now available on the use of Digital Anal Rectal Examinations (DARE) for the detection of anal cancer. Since screening can result in more harm than benefit, our objective was to assess the evidence for use of DARE as a public health screening tool.

Methods: We conducted a current critical appraisal of anal cancer literature using the ten World Health Organization (WHO) criteria for assessing the potential utility of a public health screening program.

Results: DARE satisfies almost all WHO screening criteria to detect early invasive anal cancer among HIV-positive men who have sex with men (MSM): 1) anal cancer is an important health problem; 2) non-controversial treatment modalities exist for invasive anal cancer; 3) resources for conducting DARE may be available in most places; 4) invasive anal cancer has a recognizable early symptomatic phase; 5) DARE may recognize common anal cancer signs and symptoms including palpable anal canal tumors and visible perianal lesions; 6) DARE is acceptable; 7) the natural history of invasive anal cancer is well understood, in comparison to the natural history of HPV infection; 8) there is agreement on whom to treat; 9) DARE is cost-effective; and 10) there is likely to be patient compliance with repeated screening. Additional sensitivity and specificity data would add support for screening among HIV-positive MSM. Among other HIV-positive and HIV-negative populations at increased risk for anal cancer, more data are also needed on DARE acceptability and cost-effectiveness.

Conclusions: Our review of WHO screening criteria supports consideration of integrating DARE into screening for HIV-positive MSM. However, need for clinician training, lack of facilities for anal cancer treatment in some areas and insufficient data on sensitivity and specificity of DARE hinder its adoption.

#0417

2 - Epidemiology and natural history

Low prevalence of high-risk anal HPV in young gay and bisexual males after the universal HPV vaccination program in Australia: findings from the HYPER2 study

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Background/Objectives: Australia introduced a school-based quadrivalent human papillomavirus (HPV) vaccination program for females in 2007. This was extended to include boys aged 12-13 from 2013, with a two-year catch-up for boys aged ≤15. This study examined HPV prevalence among young gay and bisexual males (GBM) who were age-eligible for vaccination in the school-based program.

Methods: The HYPER2 study followed the similar methodology in HYPER1 conducted in 2010-2012.[1] The HYPER2 study was a cross-sectional study of males aged 16-20 years were recruited from sexual health clinics and the community in Melbourne in 2017-2018, if they reported any form of male sexual contact, and were residents of Australia from 2013. A clinician-collected anal swab, self-collected penile swab and oral rinse were collected and analysed for HPV detection and genotyping using AnyplexTM II HPV28 Detection assay (Seegene, Seoul, Korea). We compare the site-specific HPV prevalence between men in the HYPER1 study (males were not eligible for the universal school-based program) and the HYPER2 study (males were eligible for the program).

Results: The mean age of GBM in the HYPER2 was 18.6 years. The median number of lifetime male partners was 10 [IQR 5-25] for receptive oral sex, four [IQR 1-11] for receptive anal sex and one for insertive anal sex [IQR 0-6]. Overall, 64% of men in HYPER2 received at least one dose of vaccine documented via the National HPV Vaccination Program Register. Demographic characteristics and sexual practices did not differ between the two cohorts. The anal quadrivalent HPV genotypes (4vHPV) in HYPER2 was significantly lower than in HYPER1 (9.1% vs 29.8%; p<0.001). Furthermore, the prevalence of anal HPV16/18 in HYPER2 was 6.1% which was significantly lower than HYPER1 (14.7%) (p=0.005). Similarly, the penile and oral 4vHPV was also lower in HYPER2 than in HYPER1 (penile: 16.0% vs 21.6% [p=0.152]; oral: 0.5% vs 3.5% [p=0.033]).

Conclusions: The prevalence of anal 4vHPV among young gay/bisexual men following the school-based male HPV vaccination in HYPER2 was significantly lower than in HYPER1 with similar demographic characteristics and sexual practices. The addition of male HPV vaccination to female programs may reduce the incidence of anal cancer among GBM.

References: 1. Zou H, et al. Early Acquisition of Anogenital Human Papillomavirus Among Teenage Men Who Have Sex With Men. Journal of Infectious Diseases. 2013; 209(5): 642-651.

#0527

32 - Sexually transmitted diseases and HIV infection

PREVALENCE OF HPV AND SEXUAL HEALTH AMONG SEX WORKERS AND MEN WHO HAVE SEX WITH MEN: A PROTOCOL STUDY

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Background/Objectives: HPV infection is transmitted through skin-to-skin contact, being vaginal and anal sex the most common transitions route. Sex workers and men who have sex with men (MSM) are more exposed to the virus and, therefore, a higher frequency of infection would be expected. However, studies investigating this association have shown discordant and inconclusive results. For this reason, the prevalence, infection types, forms and factors of transmissions will be investigated for controlling infection-related outcomes.

Methods: This will be a multicenter study with respondent-driven sampling (RDS) method to recruit 1,174 sex workers and 1,198 MSM from all regions of Brazil. The study will consist of a preliminary interview to verify the eligibility criteria and to characterize the network size, as well a questionnaire with sociodemographic, behavioral, and sexual information. Specimens from oral cavity, cervical or penile/scrotal sites, and anal region will be collected and participants will do a rapid test for HIV and syphilis. All HPV samples will be processed in a certified central laboratory using type specific detection using Anyplex II HPV 28 detection (Seegene®). Strict quality control will be performed using different procedures, including training and certification of health professionals responsible for data acquisition, monitoring visits, and test-retest.

Results: Due to the literature gap on the MSM and sex workers' sexual health and the intense stigma around these populations, a critical analysis of the study results will contribute to epidemiological knowledge and will be useful for the development of strategies against virus morbidities.

Conclusions: This will be the first nationwide study with uniform methodology to evaluate the prevalence of HPV and its types among these specific vulnerable population in Brazil.

#0538

2 - Epidemiology and natural history

THE PREVALENCE OF HIGH-RISK HPV DNA AND mRNA IN ANAL PAP SMEARS FROM AN OUTPATIENT POPULATION OF HIV-POSITIVE MEN WHO HAVE SEX WITH MEN IN IRELAND

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Background/Objectives: Human papillomavirus is the most common STI in the world (1). 90% of people worldwide will be infected by it throughout their lifetime. More than 80% of anal cancer is caused by infection from HPV (2). Anal cancer is relatively rare in the general population, however, HIV-positive MSM have more than 50 times the risk (3). Like in cervical cancer, anal cancer develops through characteristic epithelial precursors (4). Unlike cervical cancer, there is no internationally agreed-upon approach for screening for anal cancer (5). The rates of anal cancer in HIV-positive MSM are in the order of 70-100/100,000 (6), higher than the incidence of cervical cancer in the general female population before widespread cervical Pap screening was introduced (40-50 cases/100,000) (7). The purpose of this study is to examine the prevalence of high-risk HPV DNA and mRNA in anal pap smears of HIV positive MSM with a view to assessing their utility as a screening tool in the future.

Methods: HIV positive MSM patients were recruited to the study. Inclusion criteria for the study included patients over the age of 18 years with proficient English. A history of anal cancer and partial HPV vaccination were the major exclusion criteria. Patients were recruited at their routine HIV clinic appointments and underwent anal pap smear sampling by a clinician. The pap smear samples collected in PreservCyt, were analysed for high-risk HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) using the Cobas 4800 HPV test. High-risk mRNA (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) was detected using the Aptima HPV assay.

Results: 160 patients were recruited to the study. The patient ages ranged from 20-61 years. 64 patients (40%) were never smokers. 65 patients (41%) were born in Ireland. All patients were in receipt of antiretroviral therapy and had suppressed HIV viral loads. High-risk HPV DNA was found in 104 patients (65%) HPV 16 and HPV 18 were found in 35 (22%) and 14 (9%) patients respectively. Other high-risk HPV DNA was found in 99 patients (62%). High-risk HPV mRNA was found in 75 patients (47%).

Conclusions: This study is the largest of its kind involving HIV positive MSM patients in Ireland. The high rates of high-risk HPV infection in our cohort (65%) is consistent with similar populations worldwide. The rates of high-risk HPV mRNA was lower at 47%. These results will be used in conjunction with anal cytology to help examine the utility of new biomarkers for personalised HPV care in high risk patients.

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#0424

2 - Epidemiology and natural history

SCREENING FOR ANAL HPV IN MSM AND FOLLOW UP AFTER TREATMENT FOR ANAL CONDILOMA

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Background/Objectives: Anal infection with HPV is common in MSM and infection with multiple genotypes is not rare. There is no recent data of incidence of anal HPV infection or most common genotypes in our region and there is also no protocol on how to follow-up MSM after treatment for anal condyloma. Our goals are to: evaluate incidence and genotypes of anal HPV in MSM in our region; relate HPV genotypes to persistence or recurrence of anal condyloma; develop a protocol for screening of this population and for follow-up after treatment of condyloma.

Methods: Patients with and without anal condyloma, 18 to 50yo, were admitted and divided in these 2 groups. Liquid based cytology was collected, anal examination and HRA were performed at initial and follow-up consultations. Patients with condyloma were referred for treatment. Follow up of all patients was done 2, 6 and 12 months after initial consultation. The material collected for cytology was also sent for Linear Array HPV Genotyping Test, with identification of 37 genotypes of HPV.

Results: The study is still ongoing. Our goal is to include 120 patients and until now 56 patients with anal condyloma (64% - group 1) and 32 without condyloma (36%- group 2) were included. The mean age was 27.1yo (±6.9) in group 1 and 34 (±7.6) in group 2 ($p<0.005$). 17 (30.9%) patients in group 1 and 11 (34.4%) in group 2 were already treated for anal condyloma in the past ($p=0.47$), 13 (23.2%) patients in group 1 were HIV positive and 7 (21.9%) in group 2 ($p=0.55$). Median number of sexual partners in the past year was 5 in both groups ($p=0.72$). At baseline, cytology was positive in 47 (83.9%) of patients with anal condyloma and in 9 (28.1%) patients without condyloma. LSIL was the most common finding overall (42%) followed by ASCUS (14.8%) and ASC-H (6.8%); no HSIL were detected. Until now 40 patients had their second consultation (26 group 1 and 14 group 2) and 8 patients (6 group 1 and 2 group 2) had their 3rd follow-up. Comparing second cytology to the first, 13 patients maintained the cytology negative (10 of group 2), 23 maintained positive (19 of group 1), 3 patients became negative (group 1) and 1 patient negative at baseline became positive (group 1).Among 9 patients negative at baseline in group 1, 7 had only external condyloma at first; one patient that developed internal condyloma became positive; 3 maintained negative and did not develop new condyloma. At baseline, 13 (12.5%) of patients were positive for HPV types 16 or 18, 6 (10.7%) of patients in group 1 and 5 (15.6%) in group 2. Considering all high risk genotypes, they were present in 29 (32%) of all patients, 20% of patients in group 1 and 9% in group 2 ($p=0.49$). Presence of high risk types was also not related to recurrence or persistence of infection 2 months after treatment ($p=1.0$). Most commonly found types were: 11 (26.1%), 6 (20.5%), 51 (9.1%), 59 (8%) and 16 and 62 (6.8% each). Types 18, 39, 45 and 55 were found in 5.7% of patients.

Conclusions: Although our study is still recruiting patients, until now we found no relation between type of HPV and persistence of anal infection. We are also finding the main types found in our community, which can be helpful to estipulate preventive actions (for ex, immunization). Although 2 months seems to be a shorter interval to reevaluate HPV status by cytology after treatment for condyloma, we hope to stablish a protocol for follow up for these patients in the near future.

#0366

32 - Sexually transmitted diseases and HIV infection

A BLOOD-BASED TUMOR MARKER FOR THE EARLY DETECTION AND MONITORING OF HPV-INDUCED ANAL CANCER IN HIV-PATIENTS

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Background/Objectives: People living with HIV are at an increased risk of developing HPV16-induced anal cancer. Yet, there are currently no global anal screening programs in place and the most common diagnostic approaches require anal smears for cellular characterization. The establishment of a blood-based biomarker for the early detection and post-treatment surveillance of tumor patients would therefore be highly desirable. In this pilot study, we assessed the performance of a novel competitive serological assay for the early detection and post-treatment monitoring of HPV16-induced anal cancer in HIV-positive individuals.

Methods: This retrospective study included 12 HIV-positive patients diagnosed with HPV16-induced anal cancer and recruited though the German Competence Network for HIV/AIDS. Serum samples that had been collected before and after tumor treatment were analyzed for the presence of anti-HPV16 L1 antibodies using a newly developed, highly specific rapid test based on the HPV16-L1-specific monoclonal antibody clone DRH1 (PrevoCheck, Abviris Deutschland GmbH, Germany). DRH1 antibody levels in patient sera were monitored following treatment and correlated with clinical outcomes.

Results: All patients were men with an average age of 45 years [27-63 years] at the time of anal cancer diagnosis. The mean duration of the HIV infection was 10.2 years [5-19 years] and 11 of the patients were MSM (men who have sex with men). For 10 of the 12 patients, we had access to sera collected in the 12 months preceding tumor diagnosis. Of these, 9 tested DRH1 positive with antibody levels of 1000-3000 ng/mL. The earliest detection of HPV16-induced anal carcinoma using this assay was possible 293 days ahead of clinical diagnosis. For the remaining two patients, sera were only available at 516 and 578 days before tumor diagnosis. These sera tested DRH1 antibody negative, suggesting a positive relationship between antibody levels and tumor development. Blood sera collected up to 89 days after tumor treatment showed a decrease in DRH1 antibody levels by 25-60%, mirroring successful tumor removal. Notably, a 30% increase in antibody levels measured after treatment in one of the patients was linked to disease recurrence.

Conclusions: The rapid, blood-based test for HPV16 L1 DRH1 antibodies assessed here is easy to use and provides a test result within 20 minutes. In this retrospective pilot study, it detected HPV16-induced anal cancer in HIV-positive patients with a sensitivity of 90% and as early as 9.5 months before clinical diagnosis. Notably, test results during post-treatment follow-up were indicative of treatment outcome and disease recurrence. Serological detection of DRH1 antibodies in patient blood is therefore a highly promising novel tool for the early detection and post-treatment surveillance of HPV16-induced anal tumours.

#0252

27 - Anal neoplasia

PROGNOSTIC SIGNIFICANCE OF HPV DNA AND P16INK4A IN ANAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background/Objectives: Human papillomavirus (HPV) DNA and p16INK4a are prognostic markers in several HPV-related cancers. We conducted a systematic review and meta-analysis of observational studies evaluating survival in anal cancer patients, according to HPV DNA, p16INK4a, and combined HPV DNA/p16INK4a status.

Methods: In this systematic review and meta-analysis we searched PubMed, EMBASE, and Cochrane Library databases to identify studies published in English until July 25th 2018, directly providing or allowing estimation of survival of anal cancer patients according to the presence of HPV DNA and/or overexpression of p16INK4a. We extracted information on overall survival (OS), disease-specific survival, and progression- or disease-free survival. We pooled published hazard ratios (HRs) and 95% confidence intervals (CIs) for OS using a random-effects model. I2 statistic described heterogeneity.

Results: We included 16 studies, which comprised 1724 anal cancer patients tested for HPV DNA (65% positive), and 567 patients tested for p16INK4a (87% positive). The pooled HR for OS was 0.54 (95% CI 0.33 - 0.89) for HPV DNA-positive versus negative, 0.37 (95 % CI 0.24 - 0.57) for p16INK4a-positive versus -negative, and 0.36 (95% CI 0.22 - 0.58) for HPV DNA-positive/p16INK4a-positive versus HPV DNA-positive/p16INK4a-negative anal cancer patients.

Conclusions: Patients with HPV DNA- or p16INK4a - positive anal cancer have significantly better OS compared to HPV DNA- or p16INK4a - negative. The best OS was observed in patients who were positive for both HPV DNA and p16INK4a. This points to the possible value of HPV DNA and/or p16INK4a testing when planning the individual management and follow-up strategy for patients diagnosed with anal cancer.

FC 19 - Colposcopy / Management (I)

#0203

23 - Colposcopy

COLPOSCOPIC CHANGES OF THE CERVIX AND HIGH-RISK HPV ASSOCIATION

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Background/Objectives: BACKGROUND: It is widely accepted the association between high risk human papilloma virus (HR HPV) infection and the presence of cervical cancer and dysplasic changes on the cytology and histology of the cervical cells. But there is no information that stablishes the association of the presence of this virus with the grade of colposcopic changes, manly in the mayor ones.OBJECTIVE: To analyze the association of colposcopic changes of the cervix with the presence of high-risk human papillomavirus in women at the colposcopy clinic of Valentin Gomez Farias Hospital from January 2014 to December 2014.

Methods: A cross-sectional study was made with 394 patients who underwent sampling for typing HR HPV with a DNA PCR test (COBAS 4800 - Roche ®) and underwent colposcopic examination to identify colposcopic changes. The strength of association between the presence of high-risk HPV and colposcopy changes by OR odds ratio was determined. The results were considered statistically significant with $p < 0.05$. We also stablished the statistical agreement by Kappa coefficient.

Results: The prevalence of HR HPV infection was 14%; there was a moderate association (OR 2.9 95% CI 1.6-5.5) and a slight statistical agreement (K: 0.17) between the presence of all high-risk HPV and colposcopy changes. By subdividing HPV groups, a strong association (OR 6.8, 95% CI 1.3-35.3) and a slight statistical agreement (k: 0.13) between the HPV 16/18 and major colposcopic changes was stablished. No association was found between HPV 16 /18 infection and colposcopic changes in general (p: 0.16). A moderate association (OR 2.8 95% CI 1.4-5.3) and mild statistical agreement (k: 0.14) among the other 12 types of HPV with all grades of colposcopic changes was stablished. No association was found between infection with the other 12 pool HR HPV and major colposcopic changes (p=0.64).

Conclusions: This study demonstrates a strong association of the HPV 16/18 DNA present in cervical cells with major colposcopic changes of the cervix, but no association with minor ones. The presence of HR HPV 16/18 in patients with major colposcopic changes matches the existing association with cervical cancer, thus we can conclude that in a screening scenario, patients should be sent to a colposcopy clinic when the presence of HR HPV is 16/18, and not with the other subtypes.

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#0483

22 - Diagnostic procedures / management

Reproductive and oncological outcomes after treatment for CIN: a systematic review and network meta-analysis

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Background/Objectives: There are several excisional or ablative techniques for cervical intra-epithelial neoplasia (CIN). There is evidence suggesting that treatment for CIN increases the risk of adverse obstetric outcomes in subsequent pregnancies and that this risk is greater for more radical treatment modalities which remove a larger part of the cervix [1-2]. On the other hand, less radical treatments might compromise oncological safety [3]. However, the data is conflicting. Our aim is to compare and rank all local treatment techniques for CIN regarding risk of adverse obstetric outcomes and risk of recurrence by performing a network meta-analysis (NMA).

Methods: We identified randomised clinical trials (RCTs) and non-randomised studies (NRS) comparing the risk of adverse pregnancy outcomes or recurrence amongst different CIN treatment techniques and/or to untreated women. We searched electronic databases and trial registries, and we also hand-searched references of identified papers. Risk of bias in RCTs and NRS was evaluated by RoB 2 and ROBINS-I tool, respectively. When transitivity assumption was found to be valid (i.e. effect modifiers did not differ amongst the different treatment comparisons), a random-effects NMA was performed. In order to combine both RCTs and NRS in NMA, we used the design-adjusted model [4]. Our main outcomes were preterm birth less than 37 weeks of gestation, and treatment failure defined as any abnormal cytology [atypical squamous cells of undetermined significance (ASC-US) or worse] or histology (CIN1 or worse).

Results: The risk of preterm birth after treatment for CIN is greatest for cold-knife conisation (CKC; CKC vs general population: OR=3.32; 95% CI 2.94 to 3.74) and lowest for laser ablation (LA; LA vs general population: OR=1.33, 95% CI 0.75 to 2.38). When women with untreated CIN were used as controls, the magnitude of effect estimates decreased but ORs still remained increased with the exception of LA (LA vs untreated women with CIN: OR=0.97, 95% CI 0.77 to 1.32). More detailed results for preterm birth, as well as results for efficacy, will be presented at the congress.

Conclusions: The risk of adverse obstetric outcomes is higher for more radical CIN treatment techniques. CKC ranked first in terms of greatest risk of preterm birth, while LA ranked last. LA does not seem to increase risk of preterm birth compared to a high-risk group of women with untreated CIN.

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#0528

22 - Diagnostic procedures / management

HPV TEST OF CURE (TOC) FOR TREATED CIN IN 34,000 WOMEN - AN ANALYSIS OF SEVEN YEARS' NATIONAL DATA FROM SCOTLAND

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Background/Objectives: Scotland introduced HPV testing for test of cure (TOC) for women who had undergone treatment for CIN in April 2012. Women are recalled 6 months after treatment for both cytology and HPV testing (using the Abbott RT HPV test), and referred for colposcopy if either or both tests is abnormal (>= low grade dyskaryosis). If the colposcopy is negative, women are followed with cytology for 2 (CIN1) or 5 years (CIN2+). TOC is not performed if there is a diagnosis of micro invasive squamous carcinoma or any glandular lesion; the role of TOC in the management of these conditions is being assessed at present. At EUROGIN 2016, we reported that at initial TOC both cytology and HPV testing detect disease that the other misses and that women with successful TOC can be safely returned to routine recall. Cytological surveillance of women with a positive result at TOC and a negative colposcopy results in further disease being detected. With the move to HPV testing for screening, it is important to reevaluate the performance of TOC and the relative contributions of HPV testing, cytology and colposcopy to the overall detection of disease.

Methods: The results of the TOC process and subsequent treatment and follow-up of all women who had undergone TOC since April 2012 were extracted from the Scottish Cervical Call-Recall System (SCCRS) in June 2019, giving at least 7 years data. We assessed the prevalence of residual disease in women after successful TOC compared to the screening population, and in women with an abnormal TOC. In addition we performed extended HPV genotyping of HPV negative cases associated with high grade disease at colposcopy.

Results: 34478 TOC events have been analysed. 25841 women had a negative TOC test and were returned to routine recall. 8209 women were referred for colposcopy. The 9972 women with cytology at least 2.5 years after return to routine recall have less disease than the general screening population (4.7% vs 8.2 % respectively). 1 7136 women referred for colposcopy showed no evidence of disease and 542 women had high grade disease, 20 of whom had a negative HPV test (table 1). 18 of the 20 have undergone extended genotyping (table 2). The follow-up of women on cytology surveillance will be presented. Table 1 Outcome of women undergoing TOC FU result TOC result TOC - cytology TOC+ histology Successful (%) Abnormal (% of all positives) HPV-/cyt+ HPV+/cyt+ HPV+/cyt- Total Negative 9518 (95·4) 536 (6·5) 1310 (16·0) 5290 (64·4) 7136 (86·9) Low grade 423 (4·2) 52 (0·63) 221 (2·7) 258 (3·1) 531 (6·5) High grade 31 (0·3) 20 (0·24) 390 (4·8) 102 (1·2) 542 (6·6) Total 9972 608 (7·4) 1921 (23·4) 5650 (68·8) 8209 Table 2 Prevalence of HPV in women with HPC-/cytology+ TOC and CIN2+ Histology HPV type Negative Low risk Intermediate Risk(Group 2B carcinogens) Established High risk types (Group 1 Carcinogens) Low grade GIN 1 0 0 0 CIN2 3 2 3 0 CIN3 3 2 2 1 Squamous cancer 0 0 1 0

Conclusions: We have shown that it is safe to return women with a negative TOC test 6 months after treatment to routine cytology screening at 3 years and HPV testing is likely also to be safe. Women with positive TOC test have an increased risk of high grade disease, including invasive disease. The range of HPV types detected by current clinically validated HPV assays is appropriate for use in a TOC context.

References: 1.https://www.isdscotland.org/Health-Topics/Cancer/Cervical-Screening/

#0565

24 - Cervical neoplasia

Effectiveness of a multi-ingredient Coriolus versicolor-based vaginal gel in repairing cervical mucosa with HPV lesions. Interim analysis results of an observational study.

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Background/Objectives: Real-life studies are mandatory for complementation of RCT. They inform on the "effectiveness" of a treatment what is intended to do in routine circumstances. Objective: to evaluate the effectiveness of Papilocare® -a Coriolus versicolor-based vaginal gel- on repairing HPV-dependent low-degree cervical lesions and HPV clearance.

Methods: Observational, multicenter, prospective, one-cohort study (PAPILOBS study). Currently recruiting 300 vaccinated or not vaccinated HPV-positive women aged > 25y with pap result of ASC-US or LSIL and concordant colposcopy image during routine clinical visits in Spain. Patients are treated with Papilocare® 1 cannula/day for 21 days the first month + 1 cannula/alternate days for 5 months. After this 6-month period, patients with altered cytology and HPV persistency are treated for a 6-month extension period with the same dosage. Interim analysis of patients with normal pap smear and concordant colposcopy image (primary endpoint) and patients with HPV clearance at 6/12 months is presented. The study was approved by the ethical committee of Public University Hospital of Puerta de Hierro (Madrid). Informed consent was signed by all patients.

Results: At 6 months, data of 72 and 71 patients for pap smear/colposcopy and HPV presence, respectively, are available. 65% of patients (47/72) had negative pap smear and concordant colposcopy. HPV clearance was observed in 54% of patients (38/71). Data of 18 patients included in the 6-month extension treatment period, are available. At 12 months, 94% of patients (17/18) had negative pap and colposcopy and HPV clearance was observed in 83% of patients (15/18).

Conclusions: In this preliminary analysis, Papilocare® has shown a notable effect in both repairing HPV-dependent low-degree cervical lesions and clearing HPV, in real life conditions. Objectives can be obtained after a 6-month treatment period in most of the patients, achieving 94% extending the treatment to 12 months. These findings need to be confirmed upon study completion.

#0290

21 - Artificial Intelligence

EVALUATING THE PERFORMANCE OF AN ARTIFICIAL INTELLIGENCE CLASSIFIER ON A COLPOSCOPY POPULATION

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Background/Objectives: To assess the clinical feasibility of automated visual evaluation (AVE) of cervical images by an artificial intelligence system as an adjunct to colposcopy.

Methods: A total of N=70 patients from a colposcopy population were enrolled at 5 sites in Poland. Screening involved liquid-based cytology (LBC) and human papillomavirus (HPV) co-testing. Patients underwent standard of care colposcopy, with 1-3 images captured per patient following the application of 5% acetic acid. Colposcopic impression was also recorded, as well as HPV genotype on a subpopulation of patients. Biopsies (one or two per patient) were collected and sent for routine analysis by histopathology. The worst histopathology from each patient was used as ground truth. Positive histopathology results are indicated by cervical intraepithelial neoplasia grade 2 or above (CIN 2+). Positive cytopathology results are indicated by low-grade squamous intraepithelial lesion or above (LSIL+). HPV 16 was also assessed. Following colposcopy image capture, images uploaded automatically to a secure online image portal for retrospective analysis. The AVE classifier provides a probability of pathology for a single image, and AVE analysis was calculated per image. AVE was trained from a set of biopsy-correlated images from N=1453 patients from across the globe (US, China, Nigeria, El Salvador, Mexico, Cambodia, India, Peru, Ecuador, South Korea, and Kenya). However, no data from Poland and Europe in general were used to train the classifier, and so this analysis represents a cross-validation of this AVE version.

Results: Altogether, N=113 images were used for AVE analysis, with a resulting accuracy of 72.6%. The threshold used to determine AVE positivity was based on an optimization between the highest accuracy and the F1 scores. LBC results had an accuracy of 46.2% on N=65 adequate samples. Colposcopic impression accurately predicted positive histopathology in 42.9% of all 70 patients. Information on HPV16 was available for N=41 of the patients, yielding an accuracy of 63.4% when samples were collected. Patient enrollment is ongoing.

Conclusions: Altogether, N=113 images were used for AVE analysis, with a resulting accuracy of 72.6%. The threshold used to determine AVE positivity was based on an optimization between the highest accuracy and the F1 scores. LBC results had an accuracy of 46.2% on N=65 adequate samples. Colposcopic impression accurately predicted positive histopathology in 42.9% of all 70 patients. Information on HPV16 was available for N=41 of the patients, yielding an accuracy of 63.4% when samples were collected. Patient enrollment is ongoing.

#0411

23 - Colposcopy

TRAINING COLPOSCOPISTS USING AN ON LINE TEACHING COURSE IN ASSOCIATION WITH MOBILE COLPOSCOPY WITH QUALITY CONTROL.

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Background/Objectives: The objective is to intoduce a system into China for the teaching of colposcopy employing modern technology. Teaching colposcopy in countries that have recently adopted colposcopy is difficult. In China, a country with a vast population, a national colposcopy society was formed only five years ago and so there are are very few teachers of the technique. A system has been developed in Shanghai using an established e-learning online colposcopy course, in association with a mobile colposcope as a quality control system.

Methods: The e-learning course, developed by Professor Albert Singer of London and based on nearly 30 years of teaching, covers all aspects of basic colposcopy. It takes approximately 10 hours to complete. The mobile colposcope has been developed by Mobile ODT (Israel) and contains a high-quality photographic system with sophisticated software which includes artificial intelligence, which in turn enables an instant review of all cases seen by the colposcopist. The model system (Shanghai model) has been developed so that the online course is distributed to a number of the newly set up colposcopy centres around Shanghai. The colposcopist studies this didactic learning course and after six weeks collects a mobile colposcope. After instructions in usage the colposcopist employs them in their routine clinics. On a regular basis (daily or weekly) the colposcopic images and case commentaries are submitted to experts in China or abroad for review. This allows quality control to be a part of the diagnostic protocol. After four months the trainees will travel to Shanghai where they will be subjected to an examination both on the theoretical and practical aspects of colposcopy. Those who are successful will be given a preliminary trainer certificate which will become valid after a further six months of practice.

Results: The two parts to the colposcopy teaching system involve the online teaching course and the use of mobile colposcopy. Preliminary results show that the online teaching course has been readilly used for training. It has been accepted by two major societies (BSCCP, EFC) involved in colposcopy training. A recent study by the the BSCCP showed that just under one half of all trainees used the online course in preference to attending a traditional in-person training course. The mobile colposcope has established itself as an important tool in the management of cervical neoplasia. The incorporation of artificial intelligence into the mobile colposcope's software has improved its diagnostic ability. A recent study (1) under the auspices of the NCI has shown a sensitivity of 90% in the diagnosis of CIN2+ in the assessment of archived digitalized images taken during routine screening in a 9,400 women cohort. By the use of this system it is hoped to establish a cadre of colposcopy teachers in China.

Conclusions: In the teaching of colposcopy it is proposed that the use of an online e-learning course in association with mobile colposcopy with artificial intelligence, which allows automated visual evaluation of the colposcopic image, may help in the training of colposcopists in areas with limited or non existing colposcopy teaching. Through the use of this system it is hoped to further promote the cause of colposcopy in China.

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#0346

8 - HPV testing

ANYPLEX II HPV GENOTYPING PERFORMANCE IN THE CIN2+ MANAGEMENT AT BASELINE AND FOLLOW-UP AFTER SURGICAL TREATMENT

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Background/Objectives: HPV tests differ for technology, targets, and information on the viral load. The new generation of molecular HPV assays based on Real Time PCR display also the genotype of High Risk (HR) HPV. In this study, we evaluated the performance of the Seegene Anyplex II HPV HR (Anyplex) assay in the detection of cervical intraepithelial lesions (CIN) and as a test-of-cure in the follow-up after surgical conservative treatment.

Methods: One hundred sixty-seven women referred to the European Institute of Oncology, Milan, for surgical treatment of pre-neoplastic cervical lesions, were enrolled in this study (IEO S544) from January 2011 to June 2015. For all women a cervical sample was taken before treatment (baseline) and at first follow-up visit (range 3 to 9 months): on these samples Qiagen Hybrid Capture 2 (HC2), Roche Linear Array HPV Test (Linear Array) and cytology were performed at baseline, and HC2 and cytology were performed at follow-up. Anyplex genotyping HPV test was performed on a post aliquot from liquid-based cytology specimens. Anyplex is a multiplex Real-Time PCR assay developed by Seegene and designed to detect 14 HR HPV along with all the genotype information in a single tube. In case of positivity, Anyplex also provides the information of semi-quantitative viral load.

Results: At baseline the concordance was 94% (146/156) between Anyplex and HC2 and 93% (145/156) between Anyplex and Linear Array, respectively. At follow-up the concordance between Anyplex and HC2 was 77% (112/146); in case of discordants, all Anyplex positive and HC2 negative samples were 1+ HPV detected (low viral load). Nine women relapsed: 8 (5 HSIL, 2 LSIL, 1 ASC-H) had persistence of the same genotypes (6 HPV16, 1 HPV33, and 1HPV39), while one women tested negative not only with Anyplex but also with HC2 for the presence of a new infection by low risk genotype (HPV 72detected by Linear Array) in the sample.

Conclusions: Anyplex showed a good concordance with HC2 and Linear Array and a very good performance in CIN2+ detection. Hence, the Anyplex HPV test represents a valid option for HPV detection and genotyping in order to better stratify women for the risk of high grade lesions at baseline and to monitor patients treated for CIN2+ lesions during follow-up.

#0448

23 - Colposcopy

Colposcopic impression in a birth cohort previously eligible for HPV-vaccination

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Background/Objectives: In Sweden HPV vaccination to prevent cervical cancer started in late 2006 and in 2007. The vaccine was subsidized by around 50% for women age 13-17 years, and starting in 2012 a school based, organized HPV vaccination program for girls aged 10-12 years was launched free of charge in Sweden, together with a catch-up program for women aged 13-18 years, which was usually not school based. Vaccination coverage for subsidized HPV vaccination reached around 25-30% of the target group, and 50-60% for the catch-up program. Since the first women in Sweden eligible for vaccination entered the cervical screening program in 1993, questions on how to evaluate colposcopic and histopathologic findings have arisen. Evidence is inconsistent as to whether colposcopic features for the detection of HSIL are influenced by specific HPV genotypes (1) and there are no previous studies to our knowledge evaluating colposcopy in vaccinated and unvaccinated women from the same birth cohort entering the organized cervical screening program. As colposcopic impression may be different due to a reduction in the prevalence of vaccine-types HPV 16/18, the aim of the study was to compare the colposcopic impression between the groups.

Methods: Women in the 1994 and 1995 birth cohorts who entered in the screening program at age 23 in one region of Sweden and had a positive screening result were identified. Colposcopy was performed according to national guidelines if two consecutive tests indicated low grade lesions and HPV positivity or a single screening test indicated HSIL. Colposcopic impression was evaluated according to the Swedescore (2). Colposcopic opinion was assessed as benign, low grade, high grade or invasive. Punch biospsies were taken from colposcopic lesions and as "random biopsies" in the absence of lesions (3). An endocervical sample was analyzed for cytological findings and detection of 14 high risk genotypes using the Cobas Roche 4800 system. Histopathologic findings were used as golden standard.

Results: In 2018, 59 women from the 1994 birth cohort attended colposcopy, of which 19 (32%) reported being vaccinated. There were a total of 22 HSILs identified in the 1994 cohort. In the vaccinated group 25% (2/8) of women with HSIL had a Swedescore of 8-10 (indicating HSIL); 40% (4/10) in the unvaccinated group. Colposcopic opinion was evaluated as high grade in 75% (6/8) of women with HSIL in the vaccinated group; 70% (7/10) in the unvaccinated group.

Conclusions: Our preliminary results indicate that colposcopic examination including the Swedescore and colposcopic opinion may be useful tools also in the evaluation of vaccinated women entering the organized cervical screening program in Sweden. More results will be available at the Eurogin conference.

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FC 20 - Molecular markers (II)

#0063

12 - Molecular markers

LOXL2 expression status correlates with molecular characterization of cervical carcinoma and associates to poor cancer survival via epithelial-mesenchymal transition (EMT) phenotype

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Background/Objectives: As molecular analyses based on high-throughput sequencing developing, cancer molecular classification effectively and precisely facilitated the clinical work. This work aimed to identify a new potential therapeutic target for cervical cancer by molecular analyses.

Methods: We rewired the 176 core-set samples data from TCGA dataset, one of the largest comprehensive molecular studies of cervical cancer reported in 2017. We firstly clustered the samples into two groups corresponding to LOXL2 mRNA expression, then, combined with clinical information, HPV genotypes of samples, somatic genomic alterations and molecular subgroups to calculate the associations between them. In vitro assays verified the APOBEC3 family genes expression correlation and EMT phenotype in SiHa-shLOXL2, HeLa-shLOXL2 cell lines.

Results: There were notable correlation between LOXL2 status and cancer molecular characterization, such as somatic mutation load, HPV categories, mRNA clusters, miRNA clusters and methylation clusters. And we found that LOXL2 expression was negative correlated with the expression of APOBEC3 family genes in cervical cancer. Furthermore, we also identified that high level of LOXL2 was associated with poor overallsurvival (OS) and disease-free survival (DFS), which was associated withEMT phenotype.

Conclusions: In this study, by rewiring the TCGA cervical carcinoma data, including the clinical information, HPV status, established clusters of TCGA research network, somatic genomic alterations and APOBEC3 family genes expression, we demonstrated the correlation between the LOXL2 expression status and the molecular characterization of cervical carcinoma, and we found that LOXL2 expression status was negative corelated with the expression of APOBEC3 genes, especially APOBEC3A, APOBEC3B, APOBEC3D and APOBEC3G in vitro. More importantly, we found that increased expression of LOXL2 was significant associated with decreased survival in cervical carcinoma, which significantly associated with EMT phenotype. These data showed the clinical and molecular associations as well as functionally altered features of LOXL2 expression that may drive carcinogenesis and may serve as therapeutic target in cervical carcinoma.

#0269

12 - Molecular markers

HPV DNA integration site as proof of the origin of ovarian metastasis from endocervical adenocarcinoma: three case report

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Background/Objectives: Most endocervical adenocarcinomas are human papillomavirus (HPV)-related cancers associated with p16 immunostaining. Ovarian metastasis from cervical cancer is a rare phenomenon, the mechanism of dissemination remains unclear. The diagnosis of metastasis may be difficult to establish when the ovarian neoplasm presents features consistent with primary tumor. Immunohistochemical expression of p16 in ovarian tumors can guide the diagnosis of metastasis from HPV-related cervical cancer, but p16 positivity is nonspecific. Identical HPV genotype in the paired endocervical and ovarian tumors is a better marker for cervical origin, which may also be confirmed by identical HPV integration site.

Methods: In 3 patients with paired endocervical and ovarian tumors, HPV typing was performed on tumor DNA, isolated from formalin-fixed, paraffin-embedded (FFPE) tissue, by real-time PCR using Sybr®Green and specific HPV primers. Identification of HPV integration sites in patient 1 and patient 2 was performed on DNA isolated from cryopreserved tumor tissue by using the DIPS-PCR method. Presence of HPV and integration site in both cervical and ovarian tumors was confirmed by specific PCR followed by Sanger sequencing. Immunohistochemistry was performed for p16 on FFPE tissue sections, both nuclear and cytoplasmic staining was required for a cell to be considered "positive".

Results: Two women presented with HPV18 cervical adenocarcinoma. No signs of disease were visible on MRI after treatment. After several years of follow-up, mucinous ovarian tumors were discovered in both patients. Molecular analyses showed that the ovarian lesions were HPV18-positive; indicating a primary cervical origin. A third woman was diagnosed with grade 1 ovarian endometrioid carcinoma with no peritoneal carcinomatosis. Final histological examination and HPV genotyping revealed HPV18-related in situ endometrioid adenocarcinoma in the endocervix and HPV18-related invasive endometrioid adenocarcinoma in the endometrium and both ovaries. Additional molecular analyses performed in two patients identified the same HPV integration sites in both the ovarian and cervical tumors, confirming that the ovarian mass was a metastasis from the cervical adenocarcinoma.

Conclusions: We report three new cases of ovarian neoplasia in which the diagnosis of metastasis from cervical cancer was supported by the same HPV genotype and the same integration site in the paired cervical and ovarian tumors. To our knowledge, this is the first report of molecular evidence of the cervical origin of an ovarian metastasis. HPV screening should be performed in ovarian tumors for all patients with history of cervical neoplasia.

#0353

12 - Molecular markers

Genome wide-association study of Cervical Cancer in the UK Biobank cohort

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Background/Objectives: Persistent infection with high-risk human papillomavirus (HPV) is causally associated with cervical cancer. However, only ~1% of women with HPV infection progress to cervical neoplasia (CIN). It is estimated that heritability may explain 25-30% of total variation in liability for cervical cancer. Common genetic variants have been detected in HLA (Human Leukocyte Antigen) regions responsible for the immune response, but this is not well understood. We conducted a genome-wide association study, in two cohorts, to identify underlying genetic risk variants which might predispose to CIN and cervical cancer.

Methods: Using Northern Finland Birth Cohort 1966 (NFBC66) and Finnish nationwide registers we identified 365 women with CIN/cervical cancer and 1678 controls without a history of any cytological abnormalities. Using UK Biobank data and UK national cancer registries we identified 6378 women with CIN3/cervical cancer and 198,441 controls, this represents the largest cervical cancer GWAS to date. We conducted genome wide analyses for CIN or cervical cancer first in NFBC66 followed by UK Biobank.

Results: In the NFBC66 cohort we identified SNPs ($p<5x10E-8$) associated with increased risk of CIN or cervical cancer. Two of the top variants were associated with three protein-coding genes at the same locus: PIBF1, BORA and MZT1, all with roles in mitotic cell division and/or cancer development. In the first UK Biobank iteration we have identified potential SNPs ($p<5x10E-8$) associated with CIN3/cervical cancer, with a large number of significant loci residing within Chromosomes 2 and 6 (Figure 1). Independent loci in the Major Histocompatibility Complex (MHC) region at 6p21.3 were associated with CIN3/cervical cancer, including loci adjacent to the MHC class 1 polypeptide-related sequence A gene (MICA) and HLA-DRB1, which replicates previously reported associations from published GWAS.

Conclusions: We observed genetic variants significantly associated with CIN or cervical cancer in both cohorts. Loci within the MHC may affect susceptibility to development of CIN3/cervical cancer through altered immune responses. We will next undertake fine-mapping within the UK Biobank cohort, to determine replication of NFBC66 findings and further classify any novel causal variants that may explain the estimated genetic susceptibility to cervical cancer.

#0154

12 - Molecular markers

A novel approach of spatial preservation of cervical surface cells and the generation of biomarker cervicograms

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Background/Objectives: Screening for cervical cancer precursors is by the detection of HPV DNA/ RNA, due to its high sensitivity. However, nucleic acid presence doesn't correlate well to HSIL and has low specificity on its own. This means there is a clear requirement for a sensitive and specific HPV triage test that is superior to the current cytology triage test. The main aim of our work is to demonstrate the clinical utility of a non-invasive sampling approach (patch sampling) that preserves the spatial architecture of the cervical epithelium. This allows for the generation of biomarker cervicograms that not only identifies lesions in their entirety but also serves as an aid to colposcopy. This approach when combined with machine learning allows for objective determination of clinically relevant disease presence in a high throughput manner.

Methods: We utilise a novel patch sampling approach to obtain the cervical surface cells together with spatial preservation i.e. cells sampled for cytology. Patients attending colposcopy had a pre & post-acetic acid photo, interspersed by patch sampling. 50 patients with a high-grade smear and subsequent histology proven HSIL were recruited in one arm vs. 100 patients with LSIL. This patch was then probed with antibodies to p16/MCM (HSIL) and E4 (LSIL). The signal for each antibody was then analysed by a machine learning algorithm that generates a molecular heat-map of the cervical surface i.e. biomarker cervicogram. The result of the patch sample was compared to conventional cytology triage and to the histology result of each patient. This allowed the generation of the sensitivity, specificity, negative predictive value and positive predictive value of our approach in comparison to conventional triage tests. Finally ROCs were generated for our approach and compared to cytology triage to evaluate the accuracy of our approach.

Results: We have previously demonstrated that our approach safely samples the cells at the cervical surface while preserving the cells in their native position (Eurogin 2018). This approach of keeping cells in their native position facilitates the identification of entire p16/MCM positive (HSIL) / E4 positive (LSIL) lesions. These patterns were correlated to the underlying histology with a sensitivity to HSIL of 88%, PPV of 79% and an AUC of 86% ($p < 0.001$). This is markedly superior to that of current triage methodologies and stems from the spatial preservation of cells, which allows lesions to be identified through their close proximity to neighbouring positive cells, allowing biopsy-like information to be obtained. Finally we have trained a mixed-dense convolutional machine learning algorithm to identify such lesions which improved diagnostic objectiveness in comparison to subjective triage (cytology) and also enables analysis of patient samples in a high throughput manner which allows for quicker diagnosis.

Conclusions: Our novel non-invasive sampling approach of the cervix which preserves cells in their native position is effective in identifying HSIL. This ability to identify cells in their native context and probe them with either standard Pap staining or the biomarker panel of p16/MCM/ E4 enables objective discrimination of HSIL vs. LSIL. The approach coupled with machine learning generates a biomarker cervicogram for HPV triage, in an objective and high throughput manner, which not only improves disease detection but may also serve as an adjunct to colposcopy by enabling more precise biopsies/ treatment.

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#0228

17 - Methylation

Comparison of the performance of DNA methylation markers for the early detection of cervical lesions between Dutch and Chinese colposcopy cohorts

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Background/Objectives: Objective triage strategies are required to prevent unnecessary referrals for colposcopy in population-based screening programs using primary human papillomavirus (HPV) testing. Over the years, we have identified several DNA methylation markers with high sensitivity and specificity for detection of high-grade cervical intraepithelial neoplasia or worse (CIN2+) in women referred for colposcopy. The aim in this study was to analyze whether the diagnostic characteristics of these markers were comparable in a similar Chinese colposcopy population.

Methods: DNA methylation was assessed using QMSP for JAM3, EPB41L3, C13orf18, ANKRD18CP, ZSCAN1 and SOX1. Liquid-based cytology material was collected from 205 Chinese women undergoing colposcopy due to an abnormal cytology result (normal cervix: n=40, CIN1: n=34, CIN2: n=46, CIN3: n=49, microinvasive cancer: n=36). Diagnostic potential of 3 panels of methylation markers (C13orf18/EBP41L3/JAM3, ANKRD18CP/C13orf18/JAM3 and ZSCAN1/SOX1) was assessed and compared to previously reported data from a comparable Dutch cohort also referred to the gynecologist for colposcopy with an abnormal smear.

Results: All 6 individual markers showed enhanced methylation levels and frequency with increasing severity of the underlying lesion ($p<0.05$). Sensitivity to detect CIN2+ lesions was 79%, 76% and 72% for the 3 panels (C13orf18/EBP41L3/JAM3, ANKRD18CP/C13orf18/JAM3 and ZSCAN1/SOX1, respectively), with a specificity of 57%, 65% and 68%. For the first 2 panels these diagnostic characteristics were similar to the Dutch cohort, while for ZSCAN1/SOX1 the sensitivity was higher in the Chinese cohort but with a lower specificity (both $p<0.05$).

Conclusions: Methylation markers and their diagnostic performance were highly comparable for 2 methylation marker panels. Therefore, our methylation markers identified in a Dutch population are also applicable for triage testing in cervical cancer screening in China.

FC 21/22 - Methylation

#0554

22 - Diagnostic procedures / management

Surveillance of young HPV-positive women below age of 30 by FAM19A4/miR124 methylation: a multi-center European cohort study

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Background/Objectives: Surveillance of young HPV-positive women (age <30yr) is mainly done by cytology or HPV16/18 genotyping. Both have low specificity detecting many transient and regressive lesions. The majority of CIN2 and CIN3 lesions in these young women regress spontaneously. Classical histopathology cannot discriminate between regressive and transforming CIN lesions. This leads to considerable overtreatment. The burden of overtreatment is cumbersome because these women are in childbearing age. Therefore markers are needed to better predict high-risk for transforming disease in young HPV-positive women. Increasing methylation levels are associated with increasing CIN grade and DNA methylation status is associated with regression or progression of CIN2. The FAM19A4/miR124-2 methylation test has a very high sensitivity for cancer and detects advanced transforming CIN (i.e. with >5yr HPV infection and many copy number alterations) with a high short-term progression risk for cancer. The clinical performance of the FAM19A4/miR124-2 methylation test in young HPV-positive women (<30yr) was determined in a multicenter study to evaluate whether the test can guide the clinician in the management of CIN disease.

Methods: 1097 HPV-positive scrapes of women aged 15-29 years originating from screening and referral settings from five countries (Scotland n=204, Slovenia n=144, Denmark n=429, Germany n=155 and Spain n=139) were tested locally for FAM19A4/miR124-2 methylation (QIAsure Methylation Test). Sensitivity for histology classes was determined for methylation and HPV16/18 genotyping. In addition, 178 CIN2/3 lesions were graded based on an immunoscore combining p16INK4a, Ki67 and HPV-E4. The study is part of the Valid-screen project performed within the European Horizon2020 program.

Results: In total 98% (1071/1097) of the samples yielded valid methylation test results. Overall sensitivity rates for CIN2, CIN3 and cancer for methylation were 28.1% (47/167), 61.2% (126/206) and 100% (1/1) and for HPV16/18 genotyping 47.3%, 59.2%, and 100%, respectively. Overall specificity for ≤CIN1 and referral rates for methylation were 79.1% (551/697) and 29.9% and for HPV16/18 77.9% and 33.2%, respectively. Sensitivity for transforming lesions using the immunoscore (p16 and Ki67 strongly positive and HPV-E4 negative) was 88.6% (39/44) for methylation and 70.5% (31/44) for HPV16/18.

Conclusions: The FAM19A4/miR124-2 methylation test has a good clinical performance in women aged <30 years in different European settings and is particularly sensitive for transforming CIN lesions, which are considered to have a high short-term progression risk to cancer. The test can provide markedly better clinical management of young HPV-positive women by reducing overreferral and overtreatment.

#0354

12 - Molecular markers

The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: a systematic review and meta-analysis

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Background/Objectives: Methylation of viral DNA has been proposed as a novel biomarker for triage of HPV positive women at screening.This systematic review and meta-analysis aims to assess how methylation levels change with disease severity and to determine its diagnostic test accuracy in detecting high-grade cervical intra-epithelial neoplasia (CIN) in HPV positive women.

Methods: We performed searches in MEDLINE, EMBASE and CENTRAL from inception to September 2018. Studies were eligible if they explored HPV methylation levels in HPV positive women. Data were extracted in duplicate and requested from authors where necessary. Random-effects models and a bivariate mixed-effects binary regression modelwere applied to determine pooled effect estimates.

Results: 43 studies with 8775 high-risk HPV positive women were eligible. The pooled estimates for positive methylation rate in HPV16 L1 gene were higher for ≥CIN2/HSIL (72·7% (47·8-92·2)) vs ≤CIN1/LSIL(44·4% (16·0-74·1)). The pooled difference in mean methylation level was significantly higher in ≥CIN2/HSIL vs ≤CIN1/LSILfor the HPV16 L1 gene (11·3% (6·5-16·1)). The pooled odds ratio of HPV16 methylation in the L1 gene was 6·57 (3·49-12·39) for ≥CIN2/HSIL vs. ≤CIN1/LSIL. HPV16 L1/L2 genes performed best in predicting CIN2 or worse (pooled sensitivity 77% (63-87), specificity 64% (55-71), area under the curve (AUC) 0·73 (0·69-0·76)) (Fig1). HPV16 L1/L2 methylation improved triage of HPV16 positive women (Fig2).

Conclusions: Higher HPV methylation is associated with increased disease severity, whilst HPV16 L1/L2 genes demonstrated high diagnostic accuracy to detect high-grade CIN in HPV16 positive women. The direct clinical use of this marker in triage is limited by the need of a multi-genotype assay. Next-generation multiplex sequencing assays containing all HPV types are under development and have the potential to allow rapid, automated and low-cost methylation testing.

#0079

17 - Methylation

CERVICAL PRE-CANCER VS INVASIVE CANCER: MOLECULAR DIFFERENTIATION WITH POTENTIAL OF IMPROVING CERVICAL CANCER SCREENING

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Background/Objectives: Persistent infection with high-risk human papillomavirus (hr-HPV) is an important co-factor in cervical cancer development and is associated with DNA methylation on both human and viral genes. The S5 DNA-methylation classifier, based on target CpG sites of the human gene EPB41L3, and viral late gene regions of HPV-16,18,31 and 33 (Lorincz A et al., 2016) has demonstrated better performance for detection of cervical intraepithelial neoplasia grade 2/3 (CIN2/3) women than either HPV16/18 genotyping, cytology or combination. We tested the performance of S5 in detecting invasive cancers vs pre-cancers and quantified the degree of separation between normal/healthy, CIN3 (including in-situ carcinomas) and invasive cancer S5 scores.

Methods: Methylation status of the S5 selected CpG sites was tested in DNA extracted from exfoliated cervical cells from the UK(n=138), Spain(n=100), Colombia(n=96), Philippines(n=50), Georgia(n=42), Ethiopia(n=79), India(n=60), South Africa(n=49), Bhutan(n=60) and USA(n=200). Samples were histologically defined as normal/healthy, CIN3 and invasive cancer. DNA-bisulfite conversion was carried out and followed by pyrosequencing for the 6 components of S5. Average methylation was calculated for each marker to define the S5 score and linear regression models were defined to test the association strength between the S5 components and age or severity of disease.

Results: Methylation at all sites increased proportionally with disease severity with a Cuzick trend of $z=9.2933$ ($p<0.0001$). The separation of normal from CIN3 and from invasive cancer was highly significant (Mann Whitney test, all $p<0.0001$). Receiver operating characteristic (ROC) curves were used to assess the diagnostic potential of S5 in differentiating normal vs CIN3 and cancer patients. The are under the curve (AUC) was 0.94 (CI 95%: 0.92 to 0.96, $p<0.0001$) with a sensitivity of 93.3% and a specificity of 75%, based on a cut-off at highest Youden J index. Linear regression models showed EPB41L3 methylation to have a stronger association with disease severity $F = 367.5$ ($p<0.0001$) than age $F = 81.0$ ($p<0.0001$), indicating that methylation on EPB41L3 might have a strong potential to predict disease progression, independent of natural epigenetic methylation that occurs with age.

Conclusions: The S5 methylation classifier may be useful in cervical screening programs for differentiating normal and pre-cancers from invasive cervical cancers in women. Although the separation was very good, there is room for improvement in S5 by addition of human markers derived from an ongoing multi-omics study using Next-Generation Sequencing.

References: Lorincz, A. T. et al. Validation of a DNA methylation HPV triage classifier in a screening sample. Int. J. cancer 138, 2745-51 (2016).

#0277

17 - Methylation

A NEW METHYLATION MARKER ASSAY AS TRIAGE TEST TO IMPROVE CERVICAL CANCER SCREEENING

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Background/Objectives: In 2017 in the Netherlands, the population-based screening program for the early detection of cervical cancer has changed to primary hrHPV-testing. However, the low specificity to detect CIN2+ lesions requires triage testing. Currently, cytology is used as triage test, though it is a time consuming method and trained cytologists are necessary. Furthermore, cytology is not applicable on cervical smears collected by the self-sampler device. In the last decades, we have identified several methylation markers that might be used for triage testing. From these candidates, we identified 3 markers (ANKRD18CP, C13ORF18 and JAM3) with a very high sensitivity and specificity to detect CIN2+ and CIN3+ lesions. Our aim is to develop a multiplex quantitative methylation specific PCR (mQMSP) test and to compare the performance with a commercially available methylation test.

Methods: DNA methylation analysis was performed using mQMSP for ANKRD18CP, C13ORF18 and JAM3 with bACT as a control. Cervical scrapings were obtained from 200 women, patients referred to our outpatient clinic, with an abnormal Pap smear having either a normal cervix (n=35), CIN1 (n=64), CIN2 (n=42), CIN3 (n=48) or a micro invasive lesion (n=11). The sensitivity and specificity were compared to those obtained with the QIAsure methylation test by McNemar analysis using the same 200 samples.

Results: Methylation levels and frequencies, determined for each of the 3 individual markers (ANKRD18CP, C13ORF18 and JAM3) as well as combined in the multiplex-QMSP assay, increased with the severity of the underlying histological lesion ($p<0.0005$). The sensitivity for the multiplex assays to detect CIN2+ or CIN3+ was 74% and 88%, respectively, with a specificity of 64% and 58%. Compared to the QIAsure test, the sensitivity was similar, while the specificity of our new assay was significantly better for CIN3+ (58% mQMSP vs 48% QIAsure, $p<0.05$).

Conclusions: Our novel developed single-tube mQMSP assay showed a high specificity and sensitivity to detect CIN lesions. The specificity was better than the commercially available QIAsure test with equal sensitivity. As a triage test, our assay might reduce the number of women with false-positive test results now unnecessary referred to a gynecologist. Our novel mQMSP assay will be validated on a large cohort of women attending the population-based screening in the Netherlands.

#0419

17 - Methylation

EPIGENETIC MARKERS ALLOWING FOR EARLY RISK DETERMINATION FOR CERVICAL NEOPLASIA AND CANCER

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Background/Objectives: Cervical cancer develops slowly from lesions, so-called cervical intraepithelial neoplasias (CIN) as a consequence of persisting HPV infection. Neither at the primary HPV infection stage, nor at the manifestation of the different premalignant lesions current cervical cancer screening methods allow to distinguish between infections and lesions that will clear and those that may persist and develop into cancer. Markers with prognostic potential would allow for successful treatment of those lesions that may develop into cancer, at an early stage, which increases the chances for full cure. Whereas women with lesions that have the potential to regress, will profit from such a test, as they will not undergo long-term watchful waiting and eventual unnecessary treatment.

Methods: In a retrospective, longitudinal study cervical scrapes from 30 patients with final histopathologically assured diagnosis CIN3, for whom samples from visits even before the diagnosis CIN3 were available, were analysed for methylation of the three markers contained in the GynTect® test for cervical cancer diagnostics, ASTN1, DLX1, and ZNF671. The methylation status of the three markers was determined using methylation-specific PCR and correlated to histopathological and cytological findings.

Results: In the small longitudinal study comprising 30 patients detection (up to six years) of the markers ZNF671, DLX1, and ASTN1 was obtained in 50%, 40% and 30% of all cases at a time point where no histopathological signs of a lesion were determined. In some of these cases the markers were detected more than 2 years before CIN3 was diagnosed. In a control group comprising 552 patient samples with Pap I findings, the detection rate was significantly lower with 0.9%, 11.1% and 3.6%, respectively.

Conclusions: The results of this study underscore the prognostic value of the markers for severe cervical dysplasia. With the prospective trial GynTect-PRO we aim to confirm the prognostic value of all six GynTect® methylation markers.

#0416

17 - Methylation

A novel PAX1 methylation gene for prediction the cervical cancer:multi-center clinical research program and previous validation results

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Background/Objectives: The main purpose of the study is to verify whether the PAX1m can be as the triage biomarker for the high-risk HPV and cytology abnormal women. The second objective was to verify whether the changes of PAX1m could be used as a biomarker for follow-up after the treatments of cervical neoplasia and cancer.

Methods: Twelve hospitals, a multi-centers from Shandong Gynecological Epigenomics Alliance (SGEA), will cooperate for the study. More than 2,000 subjects will be collected and all subjects will be follow-up for one year. The study group of the Second Hospital of Shandong University is responsible for the pre-test process, clinical planning and testing verification. 217 samples were collected for the system setup including SOP of sample collection and experimental operation in labs. The methylation PAX1m gene was determined by using Hoomya methylation real-time system.

Results: A system set-up study was conducted on 217 subjects including normal uterine cervix (n=129), CIN1(n=31), CIN2(n=16), CIN3/CIS(n=26), SCC/AC(n=15) of the uterine cervix diagnosed according to histological reports in the Second Hospital of Shandong University. The result indicted that the sensitivity and specificity of PAX1m are >75% and >88%. The specificity of HPV-HR was lower than 65% with high sensitivity. The number of patients referred to colposcopy decreased more than 20%. The result shows PAX1m is a better biomarker than cytology following the HPV test as primary screening guidance in the pre-study. Four sample collection schemes have been revised as the final versions in the SGEA meeting on September 1st, 2019. All participating members sign the final project contracts and complete the confirmation of the Ethics Committee documents. The second meeting will hold at the end of this years for the goal of 600 collected samples analysis.

Conclusions: The current results indicated that the PAX1m real time PCR-based testing is promised for cervical cancer detection. The first methylation multi-center study will contribute greatly to the solution of HPV panic and inadequate colposcopy in China.

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#0447

17 - Methylation

GENOME-WIDE DNA METHYLATION PROFILING IDENTIFIES TWO NOVEL GENES IN CERVICAL NEOPLASIA

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Background/Objectives: DNA methylation analysis is a promising approach in cervical cancer screening to discriminate risk of progression along the continuum of cervical intraepithelial neoplasia (CIN) to cervical cancer. We used a pan-epigenomic approach to identify new methylation markers in cervical carcinogenesis. We aimed to determine the best performing methylation markers for risk of progression along the spectrum of lesion grades. We also evaluated the correlation between methylation levels and lesion grade (i.e., disease severity).

Methods: Physician-collected cervical samples (54 normal, 50 CIN1, 40 CIN2, and 42 CIN3) were randomly selected from women at a single-center colposcopy clinic. Extracted DNA was subjected to Illumina Infinium EPIC array analysis, and methylation was assessed blinded to histopathological and clinical data. Spearman correlation analysis was performed to determine whether DNA methylation changes correlate with lesion grade. CpG sites whose state of methylation correlates with lesion grade were assessed and a weighted DNA methylation score was calculated, comparing normal to CIN3. Methylation markers were assessed via receiver-operating characteristic curves for sensitivity and specificity as a function of methylation. Verification of identified genes was performed using a publicly available cervical cancer dataset (GSE68339, n=270). Validation of the top selected genes was performed in an independent cohort (100 normal, 50 CIN1, 50 CIN2, 50 CIN3, and 8 cervical cancer cases) of new patients, referred for colposcopic examination at three hospitals, using targeted DNA methylation Illumina amplicon sequencing. The relationship between a combined weighted score of these markers and progression from normal through precancerous lesions and cervical cancer was compared using one-way ANOVA.

Results: Our analyses revealed 7715 CpGs whose DNA methylation level correlated with progression (from normal to CIN1, CIN2, and CIN3). There was a significant trend of increased methylation with disease grade. We shortlisted a bigenic (hyaluronan synthase 1, HAS1 and ATPase phospholipid transporting 10A, ATP10A corresponding to cg03419058 and cg13944175 sites) methylation marker set; $r=0.55$, $p<0.0001$. Sensitivity and specificity were both 1.00 for detection of cancer, and verification revealed a significant positive correlation ($r=0.88$, $p<0.0001$). Validation of the four most discriminating genes (CA10, DPP10, FMN2 and HAS1) showed a significant correlation between methylation levels and disease progression (p-value <2.2x10-16, adjusted R-squared=0.952).

Conclusions: We identified methylation markers of epigenetic changes that discriminate accurately between clinically significant and transient cervical disease. Translational research of the identified genes to future clinical applications is warranted and may improve risk stratification in cervical screening.

#0469

17 - Methylation

ANALYSIS OF DIAGNOSTICALLY RELEVANT DNA METHYLATION MARKER REGIONS IN CERVICAL CANCER AND ITS PRECANCEROUS LESIONS USING NEXT GENERATION SEQUENCING

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Background/Objectives: DNA methylation, as an epigenetic mechanism, is an early and frequent event in cervical carcinogenesis. In several studies, indications were found that the degree of methylation of such marker regions may correlate with the severity of the lesion. The objective of this work is to explicitly assign the methylation of diagnostically important marker regions to tumour cells. Furthermore, the methylation level of these marker regions is investigated in relation to the severity of the lesion.

Methods: DNA recovered from manually microdissected fresh-frozen CIN and cancer tissue (CIN/tumour as well as stroma regions) was bisulfite-treated and subjected to a subsequent bisulfite-specific PCR. PCR amplicons obtained for the marker regions ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671, FAM19A4, mir124-2 and POU4F3 were sequenced for each sample on an IonTorrent PGM using the Ion 318 Chip Kit. The reads were mapped against the human reference genome hg38. In total, 64 samples from 45 patients are being examined. The samples were histologically defined as 6 CIN 1, 9 CIN 2, 18 CIN 3 and 31 cervical cancer samples.

Results: Thus far, the methylation analysis of 7 hrHPV-positive cervical cancer samples from 4 patients has been completed. In tumour areas of all samples, an average methylation over all CpGs of > 80% for the markers DLX1, SOX17, ZNF671 and mir124-2 was found. The same mean methylation level was detected in 5 of 7 samples for the markers ASTN1 and FAM19A4. Stromal cell areas served as a reference and showed an average methylation of less than 20% for most of the markers. Results for all samples will be available at the conference.

Conclusions: In the samples analysed to date, a clear assignment of methylation to the tumour regions could be made, thereby clarifying the issue that DNA methylation resides in tumour cells. The tumour cells show a 4-fold higher average methylation level compared to stromal cells for the majority of the investigated marker regions. We expect that these preliminary findings will also hold true for the remaining samples and that the increase in the methylation level of the investigated markers is related to the severity of the lesion.

#0516

17 - Methylation

VALIDATION OF HPV16 E2BS3&4 METHYLATION AS INDEPENDENT FROM GLOBAL HOST-GENOME METHYLATION AND ITS RELATION TO CLINICAL ENDPOINTS IN A COHORT OF OPSCC PATIENTS

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Background/Objectives: The HPV E2 protein is the key regulator of viral oncogene expression in HPV-driven squamous cell carcinoma including the oropharynx (OPSCC). It exerts its effect through binding at defined HPV DNA motifs in the viral upstream regulatory region (URR) in so-called E2 binding sites (E2BS). Epigenetic modification of CpG methylation in E2BS can significantly affect E2's binding affinity to its target regions and thereby provide a mechanism for functional inactivation of E2 and in turn promote carcinogenesis by uncontrolled E6/E7 oncogene overexpression. Previously we showed that methylation levels in E2BS3 and 4 in OPSCC primaries and metastases displayed a bimodal pattern and changed independently from methylation in the LINE-1 retrotransposon as a surrogate marker of global methylation during formation of metastases. Furthermore, we saw that E2BS methylation was related to clinical data such as histologic subtype and overall as well as progression-free survival. In the ongoing study we aim to validate our earlier findings from a cohort of OPSCC patients from Berlin, Germany in an independent cohort of OPSCC patients from Cologne, Germany.

Methods: We analyzed methylation levels in 4 CpGs in E2BS3 and 4 by pyrosequencing bisulfite-converted DNA from a set of 28 p16INK4a+/HPV16-DNA+ FFPE samples of primary tumors as well as 17 associated metastases from a cohort of OPSCC from Cologne, Germany. We will test for association with clinical data and compare the results obtained to our earlier cohort of 42 primary tumors with 25 associated metastases from Berlin, Germany.

Results: The overall distribution of methylation levels in both the validation cohort from Cologne as well as the previously analysed cohort from Berlin suggests the existence of at least two groups of low and high methylation in primary tumors. Median methylation in primary tumor samples including all 4 CpGs was 6 percent (range 1 to 87) with most samples showing values < 20 percent and a smaller group with levels around 80 percent. Analysis of LINE-1 methylation as a surrogate parameter of global host genome methylation and correlation of E2BS methylation to clinical parameters is currently ongoing.

Conclusions: Our preliminary results for this independent cohort of HPV-induced OPSCC indicate that E2BS3 and 4 methylation levels in HPV16's URR in OPSCC might not be randomly distributed but methylation in E2BS3 and 4 could serve a two-state, switch-like function as the presence of groups of low versus highly methylated samples suggests.

#0664

17 - Methylation

Interest of Methylation test on women with high-risk HPV and abnormal cytology

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Background/Objectives: The development of cervical cancer is due to a persistent infection with the HPV virus. Currently HPV test and cytology used for screening are either not specific enough or not sensitive enough. Those methods lacked by their inability to distinguish transitory infections from the ones that will develop into cancer. Recently, published data showed the methylation status of tumour suppressor genes FAM19A4 and miR124-2 can be used as an effective and objective tool to triage HPV positive women. It allows the detection of advanced CIN2 and CIN3 lesions leading to precancerous cells. The main aim of this study is to evaluate the performance of this new test compared to cytology and histology.

Methods: The study population of this experiment consisted of women (mean age 38 ± 1.7 years) tested positive for HPV. The laboratory receives 500 samples taken in STM medium for HC2 hrHPV test. Of these samples, 125 were detected positive for hr-HPV. These samples were tested with the QIAsure methylation assay for hypermethylation of FAM19A4 and miR124-2 tumor suppressor genes. All hr-HPV and methylation tests are performed at the ZTP laboratory, Bagnolet.

Results: Degree of infection Number of samples HC2 hrHPV Results of methylation FAM19A4 hsa-mir124-2 FAM19A4 hsa-mir124-2 FAM19A4 hsa-mir124-2 FAM19A4 hsa-mir124-2 POS NEG NEG NEG POS POS NEG POS POS CIN1 71 46 38 0 7 1 CIN2 41 37 26 2 7 2 CIN3 28 26 12 2 6 6 The frequency of methylation and the number of methylated genes increase significantly with the severity of the disease: 17,4% for CIN1 women, 29,7% for CIN2 + women and 53% for CIN3 + women.

Conclusions: These studies have demonstrated that quantifying methylation could be an effective diagnostic tool for cervical cancer. the methylation status of tumour suppressor genes FAM19A4 and miR124-2 can be used as an effective and objective tool to triage HPV positive women. It allows the detection of advanced CIN2 and CIN3 lesions leading to precancerous cells. The "QIAsure Methylation" test proved itself to be quite efficient for screening of women with high-risk HPV compared to the other existent methods. It could systematically be used as a molecular triage tool to improve screening and dispense treatment with more accuracy

#0458

17 - Methylation

MeD-seq, a novel method for genome-wide DNA methylation profiling and marker discovery for anogenital cancers

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Background/Objectives: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer, is applied to classify tumours and can predict disease outcome and treatment options.

Methods: We developed a novel method that facilitates genome-wide methylation marker discovery allowing successful identification of methylation changes associated with pre-cancer and cancer at very low cost. The assay involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE) or fresh biopsies (only 18-50ng DNA is needed). After, a DNA methylation dependent restriction enzyme digestion follows, which releases 32 base pair DNA methylated fragments that are sequenced by next generation sequencing. This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing mapping DNA methylation at more than 50% of the 30 million CpGs present in our genome. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no DNA bisulphite treatment. MeD-seq is compatible with liquid biopsies and also the low amounts of DNA derived from solid tumor tissue using laser capture microdissection.

Results: We will apply MeD-seq to investigate and understand the role of DNA methylation in healthy tissues, and to identify changes in DNA methylation associated with different stages of cervical and anal precancer and cancer such as cervical and anal squamous cell carcinoma, cervical adenocarcinoma, endometrial cancer, vulvar cancer and ovarian cancer.

Conclusions: Based on the Med-seq data, cancer-specific DNA methylation profiles are identified for these anogenital cancers and new PCR-based assays based on these profiles are developed. With the Med-Seq technology, we also tested and compared multiple regions from the same cancer sample using laser capture microdissection to identify heterogeneity within one cancer sample. Finally, we found that data generated using the MeD-seq technology was also able to confirm the presence and genotype of Human Papilloma Virus (HPV) by mapping HPV DNA sequences to different HPV reference genomes.

FC 23 - Colposcopy / Management (II)

#0223

17 - Methylation

APPLICATION VALUE OF THE ZNF582 METHYLATION GENE FOR COLPOSCOPY UNSATISFACTORY PATIENTS:PATIENTS WITH TRANSFORMATION ZONE TYPE 3

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Background/Objectives: Objectives To evaluate the efficacy of ZNF582 methylation gene as biomarkers for cervical cancer screening and triage strategy in Xiangya Hospital, China.

Methods: Methods Following the GCP guidance, the subjects were recruited in Xiangya Hospital in China. The inclusion criteria were female with age ≥20 and sexual experience with transformation zone type 3 (TZ3). The exclusion criteria included: women had history of cancer related to reproductive tract, had therapy for cervical lesions, had received HPV vaccination or at pregnancy. The ZNF582 methylation genes (ZNF582m) were collected from the residual cervical cells and determined by using Q-PCR. High-risk HPV genotyping (hrHPV) were determined by cobas 4800. Sensitivity, specificity, and accuracy for cytology, hrHPV, and methylated genes level were analyzed.

Results: Results The TZ of cervix is affected by hormone levels. The TZ moves to the cervical canal with the increase of age, fluctuation and decline of hormone levels and so on. Neither naked eye nor colposcopy can observe the complete TZ3 is unsatisfactory. Total 120 colposcopy unsatisfactory patients were recruited and analyzed in the study. The final diagnosis was confirmed by histological reports. The results showed that the ZNF582m was significantly high with CIN2 and worse lesions than those with CIN1, and normal cervix ($P<0.0001$). The sensitivity and specificity of ZNF582m (CIN2+ detection by pathology results) were both higher than 80%, respective. Compared to the efficacy of cytology results were 84% specificity but with lower sensitivity (less than 50%). The sensitivity of hrHPV was higher than 93% but with lower than 20% specificity. The pathology results of punch biopsy following colposcopy were more than 95% specificity but less than 40% sensitivity, respective.

Conclusions: Conclusion The current results indicated that the non-invasive test, the methylation Q-PCR based test (ZNF582m), is promising for cervical neoplasia CIN2+ detection for colposcopy unsatisfactory patients

#0224

31 - Genital warts

DEFINING ELIMINATION OF GENITAL WARTS - A MODIFIED DELPHI STUDY

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Background/Objectives: In Australia, high and widespread quadrivalent HPV vaccine uptake has resulted in dramatic declines in genital warts (GW) among young people. There is a real potential for elimination of GW in the near future. The World Health Organization (WHO) has recently targeted cervical cancer, a major HPV-related global public health problem, for elimination. Likewise, the WHO also highlights the importance of vaccination to achieve elimination of GW in its latest health strategy on sexually transmissible infections and encourages countries to define national targets. We aimed to reach expert consensus on proposed GW elimination targets, from a surveillance perspective, using a modified Delphi technique.

Methods: A three-phase Delphi study was conducted. Phase 1 entailed a literature review and four rounds of consultation with six Australian experts, leading to the development of a questionnaire containing preliminary elimination-related items. In phase 2, 18 national and international experts participated in a two-round Delphi workshop (rounds 1 and 2). Experts were asked to score items on a 9-point Likert scale, with 1 being strongly disagree and 9 being strongly agree. Consensus was defined as ≥70% agreement. Median and coefficient of variation (COV) were used to describe the central tendency and variability of expert responses. After incorporating experts' feedback on items that failed to reach consensus in phase 2, phase 3 was conducted via a web-based survey (round 3).

Results: There was an 89% response rate at the end of the study. A total of 10 items were rated. Eight items reached consensus at the end of the study (Table). Two items were deemed redundant in the light of emerging evidence (not shown here). The median ranged between 7.0-9.0 and COV was ≤0.30 for all items (Table). The Figure depicts the development of consensus on these items from round 1 to round 3. Consensus was reached that at ≥80% HPV vaccination coverage, GW will be eliminated as a public health problem in Australia by 2060 with a 95% reduction in population-level incidence as compared to the baseline of 2006 (including all Australian residents and recently arriving international travellers). Our results show that while major declines have already been observed in vaccine eligible people, population level elimination will take a longer time due to GW importation from countries without a quadrivalent vaccine.

Conclusions: This is the first study in the world to define GW elimination at a national level. The framework developed through this study could be used to define GW control and elimination in other settings, with targets particularly valuable for surveillance and vaccination program impact evaluation.

#0009

31 - Genital warts

GENITAL WARTS IN PREGNANCY-DIAGNOSIS AND TREATEMENT THE MOST COMMON CAUSE OF LARYNGEAl PAILLOMATOSIS IN CHILDREN UNDER 10 YEARS OLD

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Background/Objectives: HPV infection is an epidemic of modern age with the highest number of infected girls between 18 and 30 years of age and the most common diagnosis are genital warts in early or developed stage at first born women .Due to the alerted immune status during pregnancy the spreading of HPV infection is progressive .During the labor any retention of the child in the birth canal leads to aspiration of HPV particles witch further represents the most common cause of laryngeal papillomatosis in children

Methods: The study involved 60 pregnant women between 18 and 30 years of age diagnosed with genital warts in early and advanced stages that were treated with RF technique which enables the smooth vaginal delivery with no signs of HPV infection on genito-anal region. Radio wave technique involves a special combination of radio wave access evaporisation and radio wave melting. Radio wave access evaporisation causes the evaporation of HPV infected cells and by radio wave melting we get the bloodless removal of condyloma.

Results: With colposcopic examination we reveal subclinical stages of genital warts on the mucous membrane of the labia and the entrance to the vagina, and genital warts on the cervix which provides conditions for their immediate removal. The result of radio wave therapy is a bloodless surgical field with a precise and controlled removal of all forms of genital warts in one act throughout pregnancy. Operation is performed only under local anesthesia with a minimum damage to the surrounding healthy tissue, rapid recovery without accompanying infection, bleeding, recurrence, and a complete protection to the mother and fetus.

Conclusions: Genital warts during pregnancy represent a risk to the fetus during vaginal childbirth regardless of the severity of the clinical picture. Absence of colposcopic diagnosis, avoiding removing warts in the pregnancy, use of the wrong treatment leads to progress of condylomata as for outputting an infection of the fetus, by aspiration of HPV particles in the birth canal with later occurrence of laryngeal polyps in children up to 15 years. Radio wave technique removes genital warts without harmful effects on the course of pregnancy (mother-fetus) so as to avoid indicated caesarean section, and allows a smooth vaginal delivery, witch is the gold standard obstetrics.

#0473

20 - New technologies

Laser assisted Rapid Evaporative Ionisation Mass Spectrometry (REIMS) as a bedside screening tool for cervical cancer

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Background/Objectives: An average of 4.8 million liquid-based cytology (LBC) samples are collected in the UK annually as part of the cervical cancer national screening program with over £140 million in cost (1). To date, screening relied upon cytology aiming to detect precancerous cells in the exfoliated cervical cells. Cytology has limitations with moderate sensitivity (50-60%) and high false negative rates (2, 3). Cytology reporting by cytoscreeners is operator-dependent, subjective with significant inter-observer variability and consumes substantial NHS resources. Persistent infection with high-risk human papillomavirus (hrHPV) is causally associated with cervical cancer. There is Level A evidence to support that HPV DNA testing is more accurate than cytology in screening (4, 5), and this is projected to replace cytology in the UK by the end of 2019 (6). It is anticipated that this will increase accuracy but also the number of women that have a positive screening. Reflex cytology will be used to triage hrHPV positive women that need colposcopic referral.

Methods: Rapid evaporative ionization mass spectrometry (REIMS) allows interrogation of biological samples. It was originally tested coupled with standard surgical diathermy (intelligent knife: iKnife) for near-real time cancer diagnosis (7-9). The evolution of the iKnife into the use of a more refined laser beam to replace the surgical diathermy provides the new potential to explore this technology in cell pellets without the need for sample contact. The vapour with gas phase ions produced by rapid heating of the cell pellet is introduced in the spectrometer giving molecular information on the phospholipid signature. Two mL from the LBC samples were aliquoted into pre-weighted tubes and washed from the methanol-based solution before analysis with the laser REIMS. The derived spectral information was analysed to show any differentiation between hrHPV positive and negative women as well as normal, low-grade and high-grade cytology.

Results: A population of 116 women has been explored with the preliminary analysis showing that REIMS could discriminate hrHPV positive (n=58) from hrHPV negative (n=58) women with 98% sensitivity and 85% specificity. We have also demonstrated that REIMS can successfully discriminate healthy women (controls) from women with: A) any cervical pathology (borderline/low-grade squamous intraepithelial lesion (LSIL)/high-grade squamous intraepithelial lesions (HSIL)) with 89% sensitivity and 78% specificity; B) HSIL (high-grade precancer) with 93% sensitivity and 80% specificity; C) cancer with 90% sensitivity and 95% specificity.

Conclusions: Laser REIMS has many advantages over currently used hrHPV molecular tests and cytology reporting. It has the potential to offer one-stop services, eliminate human interpretation errors and observer-variability, minimise women's anxiety and reduce overburdening and cost of services through unnecessary visits.

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#0475

24 - Cervical neoplasia

Incidence of cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis

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Background/Objectives: While local treatment for cervical intraepithelial neoplasia (CIN) is highly effective to prevent cervical cancer, evidence suggests that treated women still remain at higher risk to develop cervical and other HPV-related malignancies compared to general population [1-3]. Our aim is to explore the risk of cervical cancer and other HPV- or non-HPV-related malignancies after CIN treatment.

Methods: We conducted a systematic review and meta-analysis by searching three electronic databases (MEDLINE, EMBASE, CENTRAL) up to August 2018. We included studies with centralized and at least five years of follow-up that reported on cervical or other cancer incidence or mortality after CIN treatment. Outcomes assessed were the relative (RR) and absolute (per 100,000 woman-years) cervical cancer incidence, the relative incidence of other HPV-related anogenital (vagina, vulva, anus) or non-HPV-related cancers, and mortality. Risk of bias in individual studies was assessed though QUIPS. A random-effects model was performed, and between-study heterogeneity was estimated with the Paule-Mandel method.

Results: 27 publications met the inclusion criteria. Incidence of cervical cancer after any local treatment of any grade of CIN was elevated compared to general population (RR=3.30, 95% Cl 2.57 to 4.24). Relative risk was higher for women aged more than 50 years at initial treatment (>50y: RR 7.15, 95% CI 4.75 to 10.76; <50y: 4.01. 95% CI 1.47 to 10.95) and remained elevated for at least 20 years after treatment. The pooled incidence rate was 39 (95% CI 22 to 69) cervical cancers per 100,000 woman-years. Incidence of other anogenital HPV-related cancers was also elevated: vaginal cancer: RR=10.84, 95% CI 5.58 to 21.10; vulvar cancer: RR=3.34, 95% CI 2.39 to 4.67; anal cancer: RR=5.11, 95% CI 2.73 to 9.55. Mortality due to cervical or vaginal cancer was elevated but not at statistical significance (RR 5.04, 95% CI 0.69 to 36.94).

Conclusions: Women with history of treatment for CIN remain at high risk of cervical and other HPV-related malignancies for at least 20 years after treatment. This risk is greater for women more than 50 years of age at time of CIN treatment. Prolonged cervical screening beyond the age of 60 or 65 should be considered for this high-risk subgroup of women. Increased vigilance for prevention or early diagnosis of other HPV-related cancers is also recommended.

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FC 24 - HPV prophylactic vaccines (IV)

#0515

5 - HPV prophylactic vaccines

REDUCTION IN VACCINE HPV TYPE INFECTIONS IN YOUNG WOMEN FIVE YEARS AFTER HPV VACCINE INTRODUCTION IN COLOMBIA

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Background/Objectives: In Colombia, the HPV vaccine was launched in 2012 targeting 9-14 years old girls in a mass school-based national vaccination program including a catch-up group of 14-17 years old reaching one of the highest coverage rates in the Americas initially. In this study, we evaluated the program's impact on type-specific HPV infection by comparing HPV cervical prevalence among vaccinated and non-vaccinated women from a single Colombian City, in order to provide short-term evidence of vaccine effectiveness.

Methods: This is a comparative cross sectional study 5 years after a quadrivalent HPV vaccination pilot project in a sentinel city between 2015 and 2018. Women were contacted through different communications strategies established at local health centers and educational institutions. 3465 women from 18-25 year old from Manizales were invited and 3273 were included. Type-specific HPV infection was assessed from cervical samples using a Linear Array genotyping test. HPV prevalence was compared between 1287 vaccinated and 1986 non-vaccinated women.

Results: The prevalence of vaccine HPV types was significantly lower in postvaccinated than in the prevaccinated women (4.3% vs 16.2%; p<0.000 (OR 95%CI 0.23 (0.18-0.30), corresponding to a reduction of 73.4%. Complete benefit was achieved in women vaccinated with three doses, no vaccine HPV type infection in postvaccinated was observed. An important reduction (86.4%) was observed in women vaccinated with two doses compared to one dose: 2.2%, 95%CI (2.1-2.3) vs 8.7% 95%CI (8.6-8.8) respectively (p<0.000). This reduction increased to 91.9%, when first vaccine dose was received before sexual debut. Significant evidence of cross-protection to HPV 45 but not to HPV-31 was observed. A slightly increase of nonvaccine oncogenic HPV types was found in potsvaccinated women compared to prevaccinated women (42.7% vs 38.9%; p<0.032 (OR 95%CI 1.17 (1.01-1.34), emphasizing the importance of including the nonavalent vaccine. No low-grade intraepithelial lesions (L-SIL) associated to HPV 16 were observed in postvaccinated women, and a significantly decreased from 14.8 to 5.9% to both HVP 18 and 31 and 22% to 11.8% to HPV 39 was found among women with L-SIL.

Conclusions: These results show that National HPV immunization program successfully prevents HPV 16-18 infections in sexually active young women. However, due to coverture decline in 2015 after misinformation of unrelated symptoms as side effects, it is necessary to improve coverture rates among women and continuous monitoring of vaccine impact to assess if over time, this reduction results in preneoplastic lesions and invasive cervical cancer prevention.

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#0654

5 - HPV prophylactic vaccines

Efficacy, Safety, and Immunogenicity of an Escherichia coliProduced Bivalent Human Papillomavirus Vaccine: An Interim Analysis of a Randomized Clinical Trial

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Background/Objectives: The high cost and insufficient supply of human papillomavirus (HPV) vaccines have slowed the pace of controlling cervical cancer. A phase III clinical trial was conducted to evaluate the efficacy, safety, and immunogenicity of a novel Escherichia coli-produced bivalent HPV-16/18 vaccine.

Methods: A multicenter, randomized, double-blind trial started on November 22, 2012 in China. In total, 7372 eligible women aged 18-45years were age-stratified and randomlyassigned to receive three doses of the test or control (hepatitis E) vaccine at months 0, 1, and 6. Co-primary endpoints included high-grade genital lesions and persistent infection (over 6months) associated with HPV-16/18. The primary analysis was performed on a per-protocol susceptible population of individuals who were negative for relevant HPV type-specific neutralizing antibodies (at day 0) and DNA (at day 0 through month 7) and who received three doses of the vaccine. This report presentsdata from a prespecified interim analysis used for regulatory submission.

Results: In the per-protocol cohort, the efficacies against high-grade genital lesions and persistent infection were 100.0% (95% confidence interval 55.6% to 100.0%, 0 of 3306 in the vaccine group vs 10 of 3296 in the control group) and 97.8% (95% confidence interval 87.1% to 99.9%, 1 of 3240 vs 45 of 3246), respectively. The side effects were mild. No vaccine-related serious adverse events were noted. Robust antibody responses for both types were induced and persisted for at least 42months.

Conclusions: The E coli-produced HPV-16/18 vaccine is well tolerated and highly efficacious against HPV-16/18-associated high-grade genital lesions and persistent infection in women.

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#0258

5 - HPV prophylactic vaccines

SAFETY OF THE NINE-VALENT HPV VACCINE (GARDASIL®9) IN TRANSPLANT AND HIV PATIENTS

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Background/Objectives: Immunocompromised patients, including transplant recipients and human immunodeficiency virus (HIV) infected patients, are more prone to persistent HPV-infection and have an increased risk for HPV-related complications due to immune deficiency. While HPV vaccination is proven to be very efficacious in preventing HPV infections in healthy populations, only a limited number of studies has been done in immunocompromised patients. This study investigated the safety and tolerability of a nine-valent HPV vaccine (Gardasil®9) in HIV and solid organ transplantation (SOT) patients (heart, lung and kidney).

Methods: One hundred HIV patients (age: 18-45 years) and 171 SOT patients (age: 18-55 years) who had not yet received HPV vaccination were enrolled. Gardasil®9 was administered as a 3-dose regimen at day 1, and at months 2 and 6. Systemic and injection site adverse events (AEs) and serious adverse events (SAEs) were recorded from day 1 until month 7 (1 month after the last vaccine). Prevalence of safety measures were compared to prevalence in historical controls. Data in this abstract are preliminary and contain safety analysis of 77% of the total to be administered doses and >50 % of all separate doses (99.2 % of dose 1, 74.6 % of dose 2 and 56.7 % of dose 3). Complete safety analysis will be presented at the conference.

Results: At least one AE was reported by 77.0 % of the participants over the course of the study. Vaccine-related AEs after any dose were seen in 69.1% of the participants. Most reported AEs were injection site AEs (60.5 %) and included pain (57.9%), swelling (7.9%) and erythema (9.2 %). Headache (9.2 %) was the most prevalent vaccine-related systemic AE. Most injection site AEs were mild in intensity. In HIV patients the AE profile of Gardasil®9 was generally similar to that of healthy controls. The safety profile of SOT patients was even better, as they reported significantly less injection site AEs than historical controls (56.5 % in the transplant group and 79.0 % in the historical controls, $p<0.001$).

Conclusions: Gardasil®9 was generally well tolerated in HIV and SOT patients with AE profiles comparable to those observed in healthy subjects. Injection site AEs in the SOT group were significantly less prevalent than in healthy controls.

#0454

5 - HPV prophylactic vaccines

Implementation of HPV Vaccination in a Private Women Health Clinic in Lebanon: Feasibility and Demographics

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Background/Objectives: The implementation of HPV vaccination in Middle East is hindered by multiple socio-cultural factors and the low incidence of cervical cancer and other HPV related diseases. The aim of the study is to report on the introduction of HPV vaccination in a private clinic setting in Lebanon (PCSL), the associated demographics, the rate of continuation and subsequent incidence of abnormal cytology.

Methods: Since 2007, opportunistic HPV vaccination is offered to women and their daughters at the Women's health Center (WHC) of the American University of Beirut-Medical Center (AUBMC). We retrospectively reviewed demographics of females who received HPV vaccines. For those who were sexually active available data on cytological screening was also collected.

Results: From 2007 to 2017, 1013 females were vaccinated with one of the two available HPV vaccines, 845 (83.4%) received the quadrivalent HPV vaccine and 151 (14.1%) received the bivalent HPV Vaccine. The average age of recipients was 26.23±5.78 (12-54) years. 43.2% of the ladies were 25 years old and younger whereas 49.1% were older than 25 (7.7% missing age).769/1013 (75.8%) patients received three doses while 162/1013 (16%) received two doses. 267/1013(26.3%) were sexually active at the time of vaccination and were followed up for an average of 4.5 years with Pap-smears. 33%(88) of the 267 were 25 years old and younger. Table 1 shows the age at vaccination, age at first Pap-smear and the Pap-smear results.6.8% (6/88) of women 25 years old and younger had abnormal Pap-smear Vs. 4.5%(8/179) of those older than 25 years . (P=0.418)The average abnormal cytology rate in our women health clinic at the AUBMC ranged 1.7 to 2.3 % during that same time interval (unpublished data).

Conclusions: In this observational study, we report the successful introduction of HPV vaccination into a PCSL. The rate of abnormal follow up smear is noticeable; however, longer follow-up and availability of reliable comprehensive pathology register is needed to assess the impact on genital warts and severe pre-cancerous genital lesions.

#0519

5 - HPV prophylactic vaccines

VACCINATION AGAINST HUMAN PAPILLOMAVIRUS IN WEST AFRICA : EXPERIENCE FROM SENEGAL

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Background/Objectives: To review the vaccination against human Papillomaviruses in Senegal

Methods: MATERIALS AND METHODS: This was a prospective, descriptive and analytical study with a comprehensive sampling of a population of Senegalese girls vaccinated at age 9 with the quadrivalent vaccine. The parameters studied take into account the number of girls vaccinated in each region and the adverse effects of vaccination. Data collection was done through a register that took into account The analysis of the data is done thanks to the software Epi-info version 7.

Results: RESULTS: In Senegal the target population to be vaccinated was 204235 girls aged 9 years for the year 2019. The population to be vaccinated in the first half was 183 163 girls. During the first 6 months, 166 468 girls were vaccinated, with a coverage of 89.8%. Senegal has 14 regions; the regions of Tambacounda had a vaccination coverage of 190.4%, Fatick had 174.5%, Ziguinchor scored 143.9%, Thies had 134.4%, Kolda recorded 122.6%, Kaolack recorded 107.9%, Saint Louis was 97.2%, Louga was 90.7%, Diourbel was 80.5%, Matam was 78.9%, Kedougou was 45.9%, Kaffrine was 39.5% and 25.6% respectively. and 23.7%. in Dakar and Sedhiou. No side effects were reported.

Conclusions: CONCLUSION: Vaccination against Papillomavirus is a reality in West Africa and Senegal is a pioneer in this area. Senegal's data are encouraging and the success of the vaccination depends on the awareness and commitment of providers and the community.

References: KEYWORDS: Vaccination, Papillomavirus, Cervical Cancer, Senegal

#0536

5 - HPV prophylactic vaccines

Comparing HPV vaccination modeled CIN3+ outcomes with real-world evidence

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Background/Objectives: In many countries, vaccines against human papillomavirus infections are introduced in national immunization programs. The decisions to include these vaccines were driven by favorable short term vaccine characteristics and modelling extrapolations. Nowadays, long-term efficacy data is available from clinical trials and real-world settings. Here, we compare existing model predictions with observed long-term efficacy data on the outcomes of CIN3 and cancer (CIN3+) as a step-up to model validations on CIN3+.

Methods: We performed a literature search for efficacy and effectiveness data on reductions of CIN3+ from both randomized clinical trials and real-world evidence from observational studies. In addition, literature describing HPV models assessing reductions in CIN3+ were collected. Model predicted outcomes for the different HPV vaccines were validated with the observed reductions in CIN3+.

Results: The quadrivalent vaccine showed vast overall reductions of CIN3+ in clinical trials, aligned with reductions seen in real-world settings, as, for example, recently for Australia. Modeled findings on CIN3+ for the quadrivalent vaccine were grossly in line with these reductions. The efficacy against HPV infection recently found of the 9-valent HPV vaccine was over 40% compared to the quadrivalent vaccine, indicating further reductions in the disease burden; however, long-term trial and real-world data on CIN3+ are obviously not yet available. The bivalent vaccine showed reductions in CIN3+ in clinical trial and real-world settings up to around 90%. Opposite to these findings, model-predicted reductions in CIN3+ for the bivalent HPV vaccine remain all well below 90%, despite incorporation of cross-protection in the models.

Conclusions: Current HPV vaccination models seem insufficient in providing insight in the actual clinical benefits of the bivalent HPV vaccine. Further work should be directed to better capture the vaccine efficacy on CIN3+ of the bivalent vaccine within HPV vaccination models.

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#0064

5 - HPV prophylactic vaccines

REDUCED HPV VACCINATION SCHEDULE AND THE RISK OF GENITAL WARTS - A POPULATION-BASED STUDY

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Background/Objectives: Since 2014, human papillomavirus (HPV) vaccination has been recommended in a reduced 2-dose schedule to girls 14 years and younger. Our group has previously reported nationwide, population-based data showing no statistically difference in effectiveness of HPV vaccination on the risk of genital warts (GWs) between girls receiving 3 and 2 doses with optimal dosing interval (1). Increasing evidence now suggests that 1 dose may provide sufficient protection against HPV-related disease (2, 3). In this nationwide, register-based cohort study, we provide further surveillance on the risk of GWs after fewer than 3 vaccine doses.

Methods: All Danish women born 1985-1999 and living in Denmark on 1 October 2006 were identified and individual-level data on vaccination were retrieved. The cohort was followed for first occurrence of GWs (redeemed prescription for podophyllotoxin and/or clinical diagnosis) up until 31 December 2016. Using Poisson regression, we calculated incidence rates (IRs) of GWs per 100,000 person-years and incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) for GWs, according to vaccination status. Analyses were adjusted for attained age and socioeconomic status. To account for prevalent HPV infection at time of vaccination, we included a 1 month buffer period. The number of vaccine doses was assessed in a time-varying manner, allowing women to contribute person-time to multiple dose categories during follow-up.

Results: The cohort comprised 481,761 females, of which 392,237 were vaccinated. The median length of follow-up was 10.2 years with 22,001 incident cases of GWs. For girls who were first vaccinated at age ≤14 years, vaccine effectiveness (VE) was high and not markedly different between girls who received 1 dose (VE: 85%; 95% CI: 81%-89%), 2 doses (VE: 91%; 95% CI: 89%-92%), or 3 doses (VE: 93%; 95% CI: 93%-94%), compared to unvaccinated women. In women initiating vaccination at age 15-18 years, VE was 69% (IRR: 0.31; 95% CI: 0.26-0.38), 75% (IRR: 0.25; 95% CI: 0.22-0.29), and 86% (IRR: 0.14; 95% CI: 0.13-0.15) for those who received 1, 2, and 3 doses, respectively, and compared to unvaccinated women. At ages older than 18 years at first vaccination, VE decreased markedly in all dose groups.

Conclusions: In this nationwide study, we find that the effectiveness of 1 or 2 dose HPV vaccination was similar to vaccination with 3 doses in preventing GWs among girls initiating vaccination before 15 years of age. Analyses are ongoing and before the EUROGIN conference, we will add calendar time to the analysis to take herd protection into account.

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FC 25 - Viral and molecular biology

#0047

1 - Viral and molecular biology

Polymorphism of TP53 as the Background of Persistent Human Papillomavirus Infection

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Background/Objectives: Approximately 200 different human papillomaviruses (HPVs) have now been characterized, and new types are regularly added to this list. These viruses can be classified into mucosal and cutaneous HPVs. Within each of these HPV groups, individual viruses are designated high risk or low risk according to the propensity for malignant progression of the lesions that they cause. HPV encodes a series of proteins, designated as early (E1-E7) or late (L1 and L2). Although all of the viral proteins have a role in viral replication, only a small number of the viral early proteins have a role in cellular transformation. Key to this process are the E6 and E7 oncoproteins, those inhibit apoptosis and stimulate cell cycle progression by binding/inhibiting the TP53 gene product. Somatic inactivation of TP53 by mutation is the most common genetic alteration in cancer and often results in functionality compromised p53 unable to efficiently induce transcription and to suppress tumorigenesis. Besides mutations, genetic polymorphisms in TP53 could also affect some of its functions. The polymorphism at codon 72 of the TP53 gene is discussed as a possible determinant for cancer risk.

Methods: 5 ml of peripheral blood were obtained by venipuncture and collected in EDTA tube from 1000 females of reproductive age (25-60 years). All of them were informed about the project, the informed consent has been obtained. From all samples there were isolated DNA by using DNA extraction kit (Qiagen). The DNA has been used for HPV Detection and Genotyping (MPCR Amplification kits were used) and determination of TP53 polymorphism at codon 72. The status of the TP53 Arg72Pro was determined by using BstUI restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR).

Results: The polymorphism at codon 72 of the TP53 gene is discussed as a possible determinant for cancer risk. It is well known, that in HPV-infected cases, the E6 oncoprotein binds to p53 protein and promotes its degradation through an ubiquiting proteolytic system altering the p53 activity in some processes, such as tumorigenesis, transcription regulation, telomerase activation, and apoptosis, thus resulting in deregulation of the cell cycle. It has been revealed, that the Arg72Arg genotype correlates with positive results of HPV genotyping.

Conclusions: We conclude, that specific genes polymorphism is essential background for HPV productive infection development and that TP53 Arg72Arg genotype is related to a higher risk of cancer development when compared to the Pro72Pro genotype.

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#0059

1 - Viral and molecular biology

HPV-CCDC106 integration alters local chromosome architecture and hijacks an enhancer by remodelling the 3D genome structure in cervical cancer

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Background/Objectives: The integration of human papillomavirus (HPV) DNA into the human genome is the reputed key driver of cervical cancer. However, the effects of HPV integration on the chromatin structuralorganization and gene expression are largely unknown in cervical cancer.

Methods: We investigated a cohort of 61 samples with clinical diagnose for integration analysis. And selected a fresh cervical cancer tissue from the corhort whose tissue only contained unique integration loci at CCDC106 and contained no HPV episomal DNA. A combination of WGS, RNA-seq, ChIP-seq and Hi-C data analysis was applied to identify the mechanisms of HPV integration in cervical carcinogenesis.

Results: Our clinical samples analysis showed that HPV frequently integrated into chromosome 19, particularly inside the CCDC106 gene. Transcriptome analysis showed that the expression of the CCDC106-HPV fusion gene was much higher than that of the CCDC106 gene without HPV integration. By generating the cervical cancer tissue and normal cervix epithelium Hi-C data, we found that the changes in gene expression between the cervical carcinoma with HPV-CCDC106 integration and normal cervical epithelium were correlated with the changes in the three-dimensional chromatin structure. More importantly, HPV-CCDC106 integration divided one topologically associating domain (TAD) into two TADs and hijacked an enhancer from the tumour suppressor gene PEG3 to the CCDC106 gene, which led to dysregulation of the PEG3 gene and high expression of the CCDC106-HPV fusion gene. Additional 10 biopsy samples with HPV-CCDC106 integration confirmed that HPV-CCDC106 integration upregulated CCDC106 expression and downregulated PEG3 expression.

Conclusions: In this work, we found thatHPV-CCDC106 integration altered local chromosome architecture and hijacked an enhancer by remodelling the 3D genome structure in cervical cancer.

#0185

1 - Viral and molecular biology

HPV-POSITIVE CERVICAL CARCINOMA CELLS - THE EFFECTS OF HPV COPY NUMBER AND IRRADIATION ON THE INVASION IN THE HUMAN MYOMA TISSUE BASED EXTRACELLULAR MATRIX MODELS

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Background/Objectives: The aim of this study was to investigate the invasion of human papillomavirus (HPV) positive human cervical cancer cell lines in human leiomyoma-based extracellular matrices in vitro, and to see if the HPV copy number and/or the irradiation affect the depth and total invasion area of the cells.

Methods: Commercially available HPV positive cervical carcinoma cell lines SiHa and CaSki, and oral squamous cell carcinoma cell line HSC-3 cells (as a positive control) were used for the cultures. CaSki cells contain around 600 copies of HPV16 virus in the genome, whereas SiHa have only 1-2 copies per cell. HSC-3 cells are HPV negative. Cells were cultured in two different human tumor extracellular matrices (3D myoma disc model, and Myogel Transwell vertical invasion assay). Cultures were irradiated with 4 Gy. Myoma invasion area and the depth of invasion were measured with ImageJ 1.51j8 software. Statistical analyses were performed with SPSS Statistics (IBM SPSS® Statistics 25).

Results: All cells invaded within myoma discs and through Myogel coated Transwell membranes. In myoma discs, a difference in the invasion depth ($p=0.0001$) but not in invasion area ($p=0.310$) between the HPV positive cell lines was seen: SiHa (less HPV) invaded slightly better than CaSki (more HPV). Slight difference in invasion depth was observed when compared HPV positive cell lines to HSC-3 ($p=0.048$), as HPV negative HSC-3 cells invaded better than HPV positive cells. No difference was detected in the invasion area ($p=0.892$) between HPV positive and HPV negative cells. The ionized radiation significantly reduced the invasion depth of HSC-3 ($p=0.001$), SiHa ($p=0.0001$) and CaSki ($p=0.001$). No effect on invasion area were detected in any cell lines; HSC-3 ($p=0.095$), SiHa ($p=0.167$) andCaSki ($p=0.095$). Significant difference was observed between SiHa and CaSki in thereduction of the invasion depth after radiation ($p=0.013$) as with SiHa the reduction was greater than with CaSki cells, but no difference in the invasion area was detected ($p=0.222$).

Conclusions: Both solid and gelatinous human uterine leiomyoma-based extracellular matrix models were usable platforms to study the invasion of HPV positive cervical carcinoma cell line cells in vitro. Cells with less HPV copy number (SiHa) invaded slightly better and were slightly more sensitive to irradiation than cells with a high copy number (CaSki). However, the HPV copy number did not drastically impact to the invasion properties of the uterine carcinoma cells.

#0566

1 - Viral and molecular biology

Protamine Sulfate Potently Reduces HPV Infection by Preventing Attachment to Heparan Sulfate Proteoglycans

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Background/Objectives: Despite advances in our understanding of how HPVs initiate infection, the molecular mechanisms governing HPV uptake into cells are incompletely understood. As an initial step, HPV particles attach preferentially to host human keratinocytes and their associated extracellular matrix (ECM) via heparan sulfate proteoglycans (HSPGs). A prevailing model of HPV entry suggests that HPV virions dissociate from HSPGs before engagement with the cellular entry receptor complex and virion uptake is proposed to be an HSPG-independent event [1]. However, work from our lab indicates that HPV infection initiation requires the release of HPV particles from cells and ECM in complex with HSPGs and growth factors [2, 3]; we refer to these virions as "HSPG-decorated HPV particles". Studies in our lab are aimed at understanding the precise role that HSPGs play in HPV infection.

Methods: We tested the efficacy of protamine sulfate (PrS), an inexpensive and clinically-used heparin antagonist, in preventing HPV infections in cell culture and animal model systems. Utilizing pseudovirions (PsVs), quasivirions and tissue-derived virions of diverse HPV genotypes, we evaluated the ability of PrS to inhibit HPV infection of HaCaT human keratinocytes and in the murine vaginal challenge model. PsV infections were determined by luciferase quantification. Virion infections were assessed using RT-qPCR to quantify spliced HPV E1^E4 mRNAs. We also tested PrS activity against other intracellular pathogens that are reported to use HSPGs for cell attachment and infection.

Results: PrS is a non-toxic and potent inhibitor of HPV infection in vitro with an IC50 of ~100nM, which is well below the typical clinical dose as a heparin antagonist in humans. PrS was effective in neutralizing HPV infection over a physiologically-relevant pH range and in the murine vaginal challenge model in vivo. PrS provided prophylactically to cells prevents HPV particle binding to the cell plasma membrane and the ECM. PrS also prevents viral attachment and neutralizes infection when HSPG-decorated HPV particles were exposed to the drug. PrS added after HPV binding did not cause virion release from cells, but remained strongly inhibitory to infection, even when added hours after infection. Initial data suggest that when PrS inhibits infection after HPV virions are bound to cells, the virions are still taken up by cells, presumably into a degradation pathway. Lastly, preliminary data suggest that PrS can reduce infection by Chlamydia trachomatis, a wide-spread human pathogen that also requires HSPG interactions for infection.

Conclusions: Our studies show that PrS is a safe and potent inhibitor of HPV infections in vitro and in vivo. We show that HSPGs can be targeted to potently prevent infections by a variety of HPV genotypes, and potentially other intracellular pathogens that require HSPG interactions during infection. The mechanisms by which PrS interferes with not yet completely defined. PrS appears to block initial HPV interaction with cell surface HSPGs and to prevent HSPG-interacting HPV from proper engagement with the requisite infection receptor(s). PrS remains highly active at a low pH, boding well for clinical utility and testing in the vaginal tract. Lastly, the low cost of PrS may make it a useful prophylactic in settings where vaccination strategies remain challenging.

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#0652

3 - Pathogenesis

The effect of demethylation on proliferation and signaling pathways of cervical cancer cells

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Background/Objectives: After treatment with 5-Aza-CdR, the proliferation of Hela, Siha, C33A, HPV16, HPV18E6 mRNA levels of cervical cancer cell lines and the expression of p21 and p53 proteins were observed.

Methods: After intervention with different concentrations of 5-Aza-CdR in cervical cancer Hela, Siha and C33A cell lines for 7 days, the proliferation changes of the three kinds of cells were detected by CCK8. Changes in HPV16,HPV18 E6 mRNA and TERT mRNA expression were detected by RT-PCR. Protein expression of p21 and p53 was detected by Western blot.

Results: The methylation level of PAX1 was expressed from high to low in Siha, Hela and C33A respectively, while the methylase level of the three cell lines was on the rise vice versa, with statistically significant differences ($P < 0.05$).With the increase of 5-Aza-CdR concentration, the proliferation inhibition of Hela, Siha and C33A cells increased, showing a dose-dependent relationship.After demethylation, the levels of HPV16E6 in Siha cells and HPV18 E6 in Hela cells showed a downward trend, while the levels of TERT mRNA in Hela, Siha and C33A cells all showed a downward trend.After demethylation, p53 and p21 protein contents in Siha, Hela and C33A cells of cervical cancer were significantly increased.

Conclusions: There were differences in the levels of PAX1 methylation and related methylase in different cervical cancer cell lines with different HPV states. Methylation inhibitors inhibit TERT mRNA levels by activating p53 and p21 signaling pathways, thereby inhibiting HPVE6 levels and inhibiting cervical cancer cell growth.

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#0705

33 - Conventional therapies

Inhibition of HPV-18 DNA Replication by Novan-1000, a Novel Nitric Oxide Releasing Compound, in Epithelial Tissue Cultures of PHKs

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Background/Objectives: For all people who have HPV or will acquire HPV infections, therapeutic interventions are essential. Early detection immediately followed by effective, safe and affordable treatment is the optimal medical care and long term public health policy. NVN1000, a proprietary compound of NOVAN Inc., releases nitric oxide (NO) from a polymeric macromolecule when transferred to an aqueous environment. Nitric oxide has diverse antimicrobial activities. It has cleared Phase 1 safety and tolerability clinical trials for topical dermatological indications.

Methods: In this study, we tested the efficacy of NVN1000 against HPV-18 genomic DNA amplification in organotypic raft cultures established with primary human keratinocytes. NVN1000 was delivered topically to the cultures for one hour daily over 6 consecutive days. Harvested rafts were probed by immunoblots and by in situ assays. Viral DNA amplification was quantified by real time qPCR.

Results: At 2 mg/ml, NVN1000 abrogated amplification of HPV-18 DNA and the synthesis of major capsid protein L1. Immunoblots showed that the E6 oncoprotein level was reduced and p53 tumor suppressor protein was significantly elevated relative to the vehicle-treated control cultures. The E7 protein and E7-induced suprabasal S-phase reentry were also significantly diminished. Based on gamma-H2AX and TUNEL signals in suprabasal strata of the HPV-18 infected cultures, NVN1000 induced DNA damage and apoptosis, whereas g-H2AX signals were much lower in uninfected control rafts. NVN1000 also caused DNA damage and apoptosis in raft cultures of PHKs transduced with recombinant retroviruses expressing HPV-16 E6 and E7 proteins.

Conclusions: These results indicate that NVN1000 is a most promising candidate for treating pre-neoplastic HPV infections. Current activities involve optimization of treatment protocols, in preparation for designing future clinical trials.

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#0050

1 - Viral and molecular biology

DIAGNOSTIC ACCURACY OF ZNF582 HYPERMETHYLATION FOR CERVICAL CANCER PRECURSOR LESIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background/Objectives: Cervical cancer presented, in 2012, 528,000 new cases in the world and around 85% of global burden occurs in countries of low to medium income. Recent studies have brought the possibility of applying epigenetic markers in cancer screening, and the best-known of them is DNA methylation. We conducted this systematic literature review and meta-analysis to evaluate the accuracy of ZNF582 hipermethylation as a biomarker for the diagnosis of cervical cancer precursor lesions.

Methods: A search was conducted in the databases Pubmed, LILACS, Embase and Cochrane Library for relevant publications from 1990 to August 2018. The search was performed using the following keywords: "Uterine Cervical Neoplasms" OR "Cervix Cancer" AND "Zinc finger protein 582" OR "ZNF582". There were no limitations regarding the publication language. We included cross-sectional studies that evaluated the presence of hipermethylation in the ZNF582 gene in women with CIN3 + confirmed by histopathological examination. The initial amostra included mainly women with abnormal cytology, characterizing a secondary screening.

Results: The survey identified a total of 734 studies, a total of 9 studies were analyzed in full text. Of these studies, 4 articles meet the criteria, representing 870 women. The ZNF582 assay showed a pooled sensitivity of 72.0% (95% CI: 65.9-77.5), a pooled specificity of 80.9 % (95% CI: 77.6-83.9), AUC of 0.8281, and DOR of 11.92 (95% CI: 5.89-24.10).

Conclusions: Our study showed that there is a high correlation between the presence of hypermethylation in the ZNF582 gene and precursor lesion or cervical cancer (NIC3+), indicating this test as a promising biomarker for cervical cancer screening. However, larger studies, comparing hipermethylation in ZNF582 with biomarkers already implemented and wellknown, preferably true randomized diagnostic trials and cost-efectiveness researchs are necessary to establish the hipermethylation of ZNF582 gene as a biomarker better than which ones that are in use.

FC 26 - Immunology

#0093

4 - Immunology

THE IMMUNE LANDSCAPE IS A STRONG PREDICTIVE BIOMARKER FOR CLINICAL OUTCOME IN EARLY STAGE VULVAR CANCER, IRRESPECTIVE OF HPV OR P53 STATUS

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Background/Objectives: Vulvar squamous cell carcinoma (VSCC) consists of three subtypes; HPV-related, HPV-negative TP53 wildtype and HPV-negative mutated TP53 (HPVposVSCC, HPVnegVSCC/p53wt, and HPVnegVSCC/p53abn, respectively) which are all treated by mutilating radical surgery and/or (chemo)radiotherapy. Despite the fact that the immune system plays a key role in cancer, the knowledge on its effect in VSCC is limited at best. A study, elucidating the clinical impact of tumor-immunity in VSCC was, therefore, performed with the aim to foster the development of immunotherapeutic approaches.

Methods: Sixty-five patients with early-stage VSCC were categorized based on HPV and p53 status. Archived tissues were analyzed for expression of CD3, CD8, FoxP3, PD-1, and pan-keratin in randomly selected areas using immunofluorescence. Additional phenotyping of T cells was performed ex-vivo on VSCC and blood samples by flow cytometry. Healthy vulvar tissue and blood served as controls.

Results: T-cell infiltration of VSCC was highly variable between patients, ranging from completely absent to very high numbers, and differed per VSCC subtype. Approximately 80% of the HPVposVSCC showed high T-cell infiltration, followed by 60% of the HPVnegVSCC/p53wt, and 40% of the HPVnegVSCC/p53abn. Importantly, high T-cell infiltration and in particular T helper cells, were associated with longer recurrence-free period and overall survival, irrespective of the HPV and p53 status. In-depth analysis of tumor-infiltrating T cells with flow cytometry confirmed the tumor-specific presence of activated effector memory T cells in VSCC and revealed that most of the CD4+ and CD8+ T cells expressed PD-1.

Conclusions: This study is the first to show a strong correlation between T-cell infiltration and clinical outcome. Our data suggest the application of two immunotherapeutic strategies depending on immune phenotype. The high expression of PD-1 in T-cell infiltrated tumors alludes to anti-PD1 blockade. While VSCC tumors with low numbers of intratumoral T cells should be stimulated with inflammatory reagents to stimulate local immune responses. This may be achieved by the use of imiquimod, oncolytic viruses or intratumoral injection with a Stimulator of Interferon Genes (STING) A specific increase of the CD4+ T-cell response could be established by the use of CTLA-4 blockade or by the agonistic antibody OX-40 in combination with PD-L1 blockade.

#0219

4 - Immunology

Impaired monocyte/immature Langerhans cell function, increased PGE2 expression, and skewed HPV6/11 adaptive immunity in RRP

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Background/Objectives: The immunosuppressive microenvironment in HPV6/11 induced, premalignant respiratory papillomas supports persistent disease and recurrence in recurrent respiratory papillomatosis (RRP) patients. Polarized TH2-/Treg adaptive immunity in blood and in papillomas containing increased immature Langerhans cells (iLC), and COX-2/PGE2 overexpression in the upper airway characterizes RRP. Here we more completely characterize RRP innate dysregulation.

Methods: Monocytes/subpopulations, blood and tissue-derived iLCs were isolated, activated by IL-36γ enriched in papillomas, PGE2, PGE2+IL-36γ, or LPS, were assessed by flow cytometry. Monocyte subpopulations and iLCs were cultured with/without added PGE2 since PGE2 was increased in RRP patients' plasma. Monocyte and tissue-derived iLCs from papillomas, foreskin, and abdominal skin were analyzed for chemokine/cytokine mRNA by qPCR after isolation, in culture, and after poly(I:C)/TNFa stimulation.

Results: Patients' monocytes generated fewer iLCs and PGE2 only reduced control monocyte-iLC differentiation, CCL-1/CCL20 mRNA expression, but not affect control/patient monocyte-iLC maturation. Papilloma iLCs expressed low CCL-1, high CCL-20 expression, but did not respond to IL-36γ. Papilloma vs. foreskin or abdominal skin iLCs differed in cytokine/chemokine mRNA expression. Only papilloma iLCs expressed CCL-1 after isolation and showed baseline IL-36γ mRNA expression.

Conclusions: These differences and different tissue-derived iLC poly(I:C)/TNFa responses imply tissue-specific, iLC function. Together, impaired RRP monocyte/iLC function, in part due to increased PGE2 exposure in vivo, likely skews HPV6/11-specific adaptive immunity.

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#0520

4 - Immunology

HPV 16/18-SPECIFIC MEMORY B-CELL RESPONSES IN WOMEN 8 YRS AFTER VACCINATION

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Background/Objectives: HPV vaccines generate long lasting immunity, as evidenced by clinical studies showing protection against disease & infection, and persisting anti-VLP antibody levels up to 10 years after vaccination. Long-term antibody production is dependent on effective immunological priming leading to long-lasting plasma cell responses. There is still uncertainty about the optimal number of HPV vaccine doses, and the need for, and if so timing of, booster vaccine doses. Whereas long-lasting plasma cells reside in the bone marrow and cannot be measured directly, memory B-cells are a circulating lymphocyte subset that give rise to plasmablasts and plasma cells, and may be a marker of effective priming of long lived antibody responses. The primary aim of this study was to develop and validate a previously described memory B-cell ELISpot assay to measure HPV-16/18-specific memory B-cells in HPV-vaccinated women.

Methods: Asymptomatic healthy women aged between 18-21 years attending a sexual health clinic in York for routine screening, who had received at least one dose of an HPV vaccine, were included in the study after signing informed consent. Blood (18mL) was drawn and peripheral blood mononuclear cells were isolated and stored. ELISpots were conducted according to a Mabtech B cell protocol for total and antigen-specific IgG with wells coated with either HPV 16 or 18 VLPs @12.5mg/mL. 1x105 stimulated cells were applied to VLP-coated wells and cultured for 18-24hr @ 37°C 5% CO2. Spots were manually counted under a dissecting microscope and numbers adjusted to represent 1x105 cells. Results are expressed as percentage VLP-specific spots/total IgG spots.

Results: Eleven women were tested for responses to HPV-VLPs 16 and 18. All had received Cervarix vaccination; 7 were certain of receiving 3 doses, 1 of 2 doses and 3 were unsure. All subjects had positive antigen-specific responses on ELISpot. In 10/11 cases B-cell responses to HPV-16 VLPs were higher than to HPV-18 VLPs (16 VLP response: range = 0.37 - 1.59, median = 0.93; 18 VLP response: range = 0.18 - 1.04, median = 0.36, Mann-Whitney U-test p=0.02).

Conclusions: This community based sample of women vaccinated with Cervarix show significant levels of circulating HPV 16/18-specific memory B-cell responses at a median of 8 years post-vaccination. This is the longest interval of HPV memory B cell responses measured post-vaccination to date. The only comparable memory B-cell data is from three dose qHPV vaccinated 9-13 yr old girls measured at 7 months, and 7.5 years later our levels are ~ 60% (HPV16) and ~ 40% (HPV18) of those, attesting to long lasting HPV vaccine induced B-cell immunity.

Amber memB

#0542

4 - Immunology

High levels of monocytic myeloid derived suppressor cells expressing arginase 1 and loss of TCR-ζ chain in CD4+ and CD8+ T lymphocytes increase the risk of high-grade cervical intraepithelial lesions in hrHPV+ women.

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Background/Objectives: Women with cervical cancer present high levels of serum arginase 1 (ARG1)[1]. Downregulation of T-cell receptor CD3-ζ chain (CD3-ζ) on CD4 (CD4/CD3-ζ) and CD8 (CD8/CD3-ζ) T lymphocytes (TL), mediated by monocytic (mMDSC) and granulocytic (gMDSC) myeloid derived suppressor cells that produce ARG1 (ARG1+ MDSCs), contribute to tumor progression[3] in various types of cancer[2]. However, nothing is known about the role of ARG1+ MDSCs in cervical cancer precursor lesions. Objective: To evaluate the association of the levels of mMDSCs-ARG1+ and of CD4+/CD3-ζ and CD8+/CD3-ζ T lymphocytes with the risk of cervical cancer precursor lesions (CIN2+)

Methods: The percentages of CD4+/CD3-ζ, CD8+/CD3-ζ T lymphocytes among CD3+ cells and of mMDSCs-ARG1+ among total MDSCs (HLA-DR-/CD11b+) were estimated by flow cytometry in peripheral blood mononuclear cells (PBMCs) of age-matched, hrHPV+ women with histopathological confirmed diagnosis of high-grade [n=75 CIN2+ (51 CIN2 and 24 CIN3)] and low-grade [n=76 ≤CIN1 (40 Negative biopsy and 36 CIN1)] lesions, selected from a 2661-participants clinical trial that followed-up for 2 years women with altered cytology. Additionally, mMDSCs (CD14+/HLA-DR-) and ARG1 expression was assessed by immunohistochemistry in the epithelium and stroma of tissues of 76 (NIC2+) and 42 (≤CIN1) of these women. Median [IQR] of the percentages of circulating and tumor infiltrating (cells/mm2) cells were compared among the ≤CIN1 and CIN2+ groups by U-Mann-Whitney test. Logistic regression models adjusted by age were used to estimate the risk of CIN2+ associated to low (upper tertile) of CD4+/CD3-ζ, CD8+/CD3-ζ T lymphocytes and high (upper tertile) levels of mMDSCs-ARG1+.

Results: The median of the percentages of CD4+/CD3-ζ (39.4% [IQR: 55.62], vs. 80.8% [IQR: 26.85], p<0.001) and CD8+/CD3-ζ T lymphocytes (69.3% [IQR: 54.42], vs 90.7% [IQR: 22.33], p<0.001) were significantly lower and of mMDSC-ARG1+ (45.5% [IQR: 45.62], vs 23.7 % [IQR: 27.22], p<0.001) were significantly higher in PBMCs of women with CIN2+ than in women with ≤CIN1. The lower tertiles of the percentages of CD4+/CD3-ζ (lower tertile <70.8 %, OR: 5.96, 95% CI: 2.96-12.49) and of CD8+/CD3-ζ T lymphocytes (lower tertile <80.1%, OR: 3.41, 95% CI: 1.77-6.75) and the higher tertile of the percentages of mMDSCs-ARG1+ (higher tertile >36%, OR: 3.23, 95%CI: 1.67-6.37) were associated with increased risks of CIN2+. Not differences in the median of MDSCs in tissue was observed but the median of ARG1+ cells/mm2 were higher in epithelium (7,89 [IQR: 10.86] vs 2,96 [IQR: 5.65] cells/mm2 p<0.001) and stromal (24.34 [IQR: 35.20] vs 3.62 [IQR: 16.45] cells/mm2 p<0.001) compartments of tissues of women with CIN2+ vs. ≤CIN1.

Conclusions: Women with high percentage of mMDSCs-ARG1+ and lower percentages of of CD4+/CD3-ζ and CD8+/CD3-ζ T lymphocytes have higher risk of cervical cancer precursor lesions (CIN2+). Our results suggests that these cells are recruited before cancer progression and that may play important role in the natural history of HPV-induced lesions.

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FC 27 - HVP screening (III)

#0336

9 - HPV screening

CRUDE AND ATTRIBUTABLE RISKS OF CIN3+ DETECTION FOLLOWING MULTIPLE ROUNDS OF HPV TESTING AT KAISER PERMANENTE NORTHERN CALIFORNIA

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Background/Objectives: Human papillomavirus (HPV) testing is more sensitive than cytology for detection of CIN3+. As a result many countries are switching to primary HPV screening, despite limited long-term experience with HPV testing. To assess screening performance over multiple screening rounds we analyzed 15 years of HPV testing results at Kaiser Permanente Northern California (KPNC).

Methods: We characterized HPV testing patterns among women aged 30 to 64 years who underwent routine HPV and cytology cotesting at KPNC from 2003 until 2018. We calculated crude risks and the proportion of detected CIN3+ cases associated with each HPV testing pattern.

Results: During the observational period 1,361,581 women had a valid HPV test result, and 7,087 women had CIN3+ detected. Crude risks of CIN3+ detection were highest following HPV-positive results, particularly with repeat positivity consistent with viral persistence (7.8% following 4 consecutive positive results) and unknown preceding test results (6.0%). For women with negative results, the risk of CIN3+ detection decreased as the number of consecutive negative tests increased (0.02% for 4 consecutive negative results). For mixed patterns of positivity/negativity, an increased crude risk of CIN3+ diagnosis was associated with more recent and frequent positivity. Most CIN3+ cases (76%) were diagnosed in women who were positive at baseline; 16% were attributed to apparent newly detected infections and 3% to possible reappearing infections, with minor differences by age and across calendar time.

Conclusions: Current HPV positivity, particularly when prevalent or repeatedly positive, is associated with a higher risk of CIN3+ than other HPV testing patterns, suggesting that previous screening history may be useful in clinical management. Most CIN3+ cases are diagnosed in women who were positive at their first visit.

#0494

9 - HPV screening

HUMAN PAPILLOMAVIRUS LOAD AND GENOTYPE-SPECIFIC PREDICTION OF INVASIVE CERVICAL CANCER

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Background/Objectives: HPV-based cervical screening is a globally recommended health policy, but different HPV genotypes differ in their associated risk for cervical cancer. For optimal composition of HPV screening tests, the sensitivity and specificity for each HPV type at different viral loads should be known in a screening setting.

Methods: About one million HPV tests taken during 2006-2014 were followed for up to 10 years for incident invasive cervical cancer. HPV test results in cervical samples taken before invasive cervical cancer for 319 women and from 1,911 matched control women were compared.

Results: Detection including low viral loads resulted in markedly increased sensitivity for cervical cancer only for HPV types 16 and 18. Testing for HPV types 31, 33, 45 and 52 also increased the sensitivity for prediction of cervical cancer but detection of low viral load did not further increase sensitivity. HPV types 35, 39, 51, 53, 56, 58, 59, 66, 67 and 68 only detected occasional additional cervical cancer cases. Testing for HPV16/18 also at low viral load plus testing for HPV 31, 33, 45 and 52 at >3000 copies/ml detected 86% of cancers occuring within a year after testing compared to the 90% that were detected by testing for 16 HPV types. Specificity was greatly increased: only 6.3% of healthy women tested positive as compared to 12.5% of healthy women testing positive for the 14 HPV types that are commonly screened for today.

Conclusions: Adequate HPV screening sensitivity, with considerable increase in specificity, can be obtained by testing only for HPV16/18/31/33/45/52, with detection of low viral load required only for HPV16/18.

#0319

9 - HPV screening

GENOTYPE-SPECIFIC, PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION IS ASSOCIATED WITH INCREASED CUMULATIVE INCIDENCE RATE FOR HIGH-GRADE CERVICAL DISEASE: THREE-YEAR LONGITUDINAL DATA FROM THE ONCLARITY TRIAL.

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Background/Objectives: Current evidence suggests that genotype (GT)-specific, persistent infection with high-risk human papillomavirus (HPV) is necessary for the development of cervical precancer and cancer. The Onclarity HPV assay is clinically validated and is capable of reporting extended GT results (HPV 16, 18, 31, 45, 51, and 52 as individual results; pooled results for 33/58, 35/39/68, and 56/59/66). The three-year cumulative incidence rate (CIR) for ≥CIN2, associated with persistent-GT infection, was investigated.

Methods: 29,513 of 29,883 enrolled women, ≥25 years, had evaluable cytology and HPV results. Abnormal cytology or an HPV(+) result led to colposcopy referral (5% normal cytology and HPV(-) controls also referred) and cervical biopsy at baseline (BL). Modeling for persistence tracking was performed by determining HPV transition states over a one-year period (e.g., BL to year one) as follows: (1) no infection—maintenance of HPV(-) status (2) HPV clearance—HPV(+) switch to HPV(-) (3) new HPV infection—HPV(-) switch to HPV(+) (4) HPV persistence—GT switch (5) GT persistence—same GT. Persistence was correlated with four possible diagnoses (negative, CIN1, CIN2, and ≥CIN3); maintenance/progression occurred when a ≥CIN2 diagnosis remained ≥CIN2 or progressed to ≥CIN3. Women not treated for cervical disease were invited for annual follow up and had colposcopies/biopsies and treatment per protocol. Colposcopy referrals at years one and two occurred based on cytology (≥ASC-US); all women received colposcopy at year three. Persistence tracking was applied to women remaining in the study at years one, two, and three. Women were removed from the study upon treatment for cervical disease, but their status was carried forward in the analysis.

Results: In total, 1,973 HPV transitions with corresponding histological diagnosis were recorded. From BL to year three, 353 women had treatment for cervical disease and were discontinued from the study. Between years one and three, 71.6% of women treated at colposcopy had ≥CIN2 pathology and of those, 90.8% had GT-specific persistence (over a time period of at least one year). For all transitions (including treatment cases), the maintenance/progression ≥CIN2 rate for no HPV infection, HPV clearance, new HPV infection, HPV persistence, and GT-specific persistence was 2.2%, 0.5%, 7.0%, 8.4%, and 35.1%, respectively.

Conclusions: GT-specific persistence closely correlates maintenance/progression of ≥CIN2. Any HPV persistence (a GT switch from the previous year) poses a ≥CIN2 risk similar to a new HPV infection.

#0481

9 - HPV screening

GRADUAL IMPLEMENTATION OF HPV SCREENING IN NORWAY: RANDOMISATION AND REAL-WORLD EVIDENCE

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Background/Objectives: Norway is in the process of changing from liquid based cytology (LBC) screening every third to highrisk human papilloma virus (hrHPV) testing every fifth year for women aged 34 to 69 years. Between February 2015 and April 2018, approximately 199 000 women, living in three counties in Norway were assigned hrHPV testing or LBC screening based on even/odd day of birth. From January 2019 a gradual and partly randomized implementation of hrHPV screening was initiated to the remaining fifthteen counties in Norway with the aim of completion within December 2021. The results from LBC screening is closely compared with hrHPV screening (health service study trial number 006_2014_10_RHS).

Methods: A shift of primary cervical screening from cytology to hrHPV detection introduce a major change in the technical and logistical infrastructure for screening. Comparative and descriptive analyses of screening attendance, primary screening results (cytology/HPV status/genotype), number of screening tests and biopsies and number of cervical intraepithelial neoplasia grade 2, 3 and cervical cancer (CIN2+) are reported.

Results: For the three pilot counties, screening attendance by age was similar in HPV screening and LBC screening, being 50,5% vs 49,4% after 1st and 27,6% vs 27,6% after 2nd reminder, respectively. The proportion of screeningtest positives was 5.4% in LBC screening and 6.5% in HPV screening, and declined by increasing age. HPV16/18 were detected in 28% of hrHPVpositives. Compared to LBC screening, we observed 45% more CIN3+ in HPVscreening. Updated results for all counties will be presented.

Conclusions: HPV screening was well accepted and detected more precancers, suggesting that replacing LBC screening with HPV screening is a good strategy. Randomized implementation of HPV screening allows monitoring the performance of novel technology in reallife, reassuring the overall high performance of the program and mitigating the transition.

#0322

9 - HPV screening

PRIMARY HUMAN PAPILLOMAVIRUS CERVICAL CANCER SCREENING ALGORITHM USING ONCLARITY WITH INTEGRATED 16/18 GENOTYPING: BASELINE AND THREE-YEAR TRIAL RESULTS

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Background/Objectives: The Onclarity Trial was performed to assess the performance parameters of the BD Onclarity human papillomavirus (HPV) assay during cervical cancer screening. Baseline and three-year longitudinal performance risk values for primary screening of women ≥25 years of age, for cervical intraepithelial neoplasia, grade 3 (≥CIN3) are reported here.

Methods: At baseline, 29,513/29,883 enrolled women had evaluable cytology and valid HPV results. We modeled the current FDA-approved algorithm for primary screening whereby HPV 16/18 positive women are referred to immediate colposcopy and those positive for any of the other 12 high-risk genotypes are referred to colposcopy based on cytology triage for ≥ASC-US. Performance parameters were also determined for ASC-US triage and hybrid screening (cytology-based ASC-US triage for women ages 25-29 years and co-testing for women ages ≥30 years). Detection of adjudicated ≥CIN3 (baseline and cumulative sensitivity) and number of colposcopies/≥CIN3 were outcomes of interest. All data analysis included verification-bias adjustment.

Results: The baseline absolute risk values for any HPV(+), HPV 16, HPV 18, HPV 16/18, ASC-US/Other 12 HPV (+), and HPV (-) were 5.3%, 14.2%, 5.2%, 12.2%, 5.3%, and 0.1%, respectively, for ≥CIN3. The baseline sensitivity associated with the HPV 16/18 primary screening strategy was 72.3%; whereas the baseline sensitivity values for ASC-US triage and hybrid screening strategies were both 53.7%. The ratio of colposcopies/≥CIN3 cases detected at baseline for HPV 16/18 primary, ASC-US triage, and hybrid screening were 11.2, 11.8, and 11.8, respectively. Three-year cumulative incidence rate values for any HPV(+), HPV 16, HPV 18, HPV 16/18, ASC-US/Other 12 HPV (+), and HPV (-) were 7.5%, 18.7%, 8.0%, 16.4%, 8.8%, and 0.2%, respectively, for ≥CIN3. The three-year cumulative ≥CIN3 sensitivity associated with HPV 16/18 primary screening was 85.8% whereas the three-year cumulative sensitivity values for ASC-US triage and hybrid screening strategies were 52.1% and 73.1%, respectively. The ratio of total colposcopies/total ≥CIN3 cases detected over three years for HPV 16/18 primary, ASC-US triage, and hybrid screening was 18.3, 15.1, and 17.7, respectively.

Conclusions: Three-year longitudinal data from this trial clinically validate HPV primary screening with the Onclarity assay. Genotyping for 16 and 18 provides effective risk stratification requiring colposcopic referral, independent of cytology, under current management guidelines.

#0407

9 - HPV screening

NEW CERVICAL CANCER SCREENING PROTOCOL FOR WOMEN VACCINATED BEFORE SCREENING AGE: PRELIMINARY DATA FROM THE "CONSENSUS" STUDY

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Background/Objectives: To evaluate the high risk (HR) HPV prevalence and the individual types in women aged 25, unvaccinated or vaccinated at age 16, to investigate the best cervical cancer screening protocol.

Methods: This Italian multicentre study is based on HR-HPV primary test instead of Pap test for women aged 25, using Cobas HPV 4800 test in Florence. HPV-negative women are invited for a new screening round with HPV test at the age of 30. Cytology triage is performed for HPV-positive samples: women with normal cytology are invited for a Pap test after 3 years and, if still negative, they will be called for an HPV test at 30 years old; women with abnormal cytology (ASC-US+) are referred to colposcopy. Full genotyping of HPV-positive samples is performed with Anyplex HPV HR test.

Results: In Florence, HR-HPV positivity is 19.2% among 1477 enrolled women. HPV prevalence is higher within unvaccinated (67/235) than vaccinated women (196/1139) (28.5% vs 17.2%, p<0.01). Cytology triage analysis shows that 27.6% (54/196) and 34.3% (23/67) of positive cases in vaccinated and unvaccinated women, respectively, have an abnormal result (ASC-US+) (p=0.29). Referral to colposcopy is significantly lower among vaccinated than unvaccinated women (4.7%=54/1139 vs 9.8%=23/235, p<0.01). Comparing vaccinated to unvaccinated women, there are not HPV16 or 18 infections in vaccinated women (0% vs 7.2%, p<0.01), there is a non-significant decrease of HR-HPV no-16/18 infections (17.2% vs 21.3%, p=0.14) and a significant reduction of HPV31 prevalence (0.6% vs 4.7%, p<0.01). HPV51 (4.2%) and HPV56 (3.2%) are the most prevalent types among vaccinated while HPV51 (7.2%) and HPV59 (5.5%) among the unvaccinated group. Coinfections in the total study population are 37.5% (106/283) with no difference between vaccinated and unvaccinated (37% vs 41.8%, p=0.49).

Conclusions: Preliminary data showing a higher HR-HPV prevalence in unvaccinated women and no HPV16 or 18 infections in vaccinated women demonstrate the effectiveness of HPV vaccination. Overall, referral to colposcopy is halved among vaccinated women due to the lower HPV positivity and the lower percentage of abnormal cytology. HPV31 prevalence is significantly lower in vaccinated women confirming a vaccine cross-protection against non-vaccine types. It will be important to assess the different progression and interval for cancer development between the two groups.

FC 28 - HPV screening (IV)

#0055

9 - HPV screening

RUSSIAN FIRST HPV PRIMARY SCREENING PROGRAM IN THE REPUBLIC OF BASHKORTOSTAN IN ACTION.

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Background/Objectives: In the Republic of Bashkortostan more than 373 women a year develop cervical cancer and about 46% of this women die. Russian First HPV Primary Screening Program was initiated there in April 2019 according to latest WHO, IARC and Russian Ministry of Health recommendations for Cervical Cancer Prevention. 30.000 women of 30-39 years old have been enrolled into the screening program to be done within one year. This age group have been chosen because of its highest mortality rate. Samples were collected both for HPV and cytology at the same time. High Risk HPV (hrHPV) positive women were triaged by cytology for further referral to colposcopy.

Methods: HPV testing was performed using Hybrid Capture 2 technique (QIAGEN GmbH). Triage was performed using conventional cytology. PAP results classified as ASC-US or more severe were considered abnormal. Of the women who were referred for colposcopy, colposcopy-directed biopsies of suspicious parts of the cervix were taken for histological examination. Histology was examined locally and classified as normal, CIN grade 1, 2, 3, or invasive cancer.

Results: 30.000 women of 30-39 years old were enrolled into the screening program and 6.100 were tested. Women were invited for a screening by 14 local Centres of Female's Health. 90,7% of the women tested had an adequate hrHPV test (n=5,533) while 9,3% (n= 567) appeared to be hrHPV-positive. HrHPV-negative women were excluded from the screening for the next 5 years interval. HrHPV-positive women were triaged by conventional cytology. HrHPV-positive but cytologically negative women were recommended to return for a follow-up testing in 12 months. All hrHPV-and PAP smear positive women were referred for colposcopy

Conclusions: HrHPV-testing was more sensitive for the detection of cervical precancer and cancer than cytology, which should reduce the incidence and cervical cancer-related mortality. Centres of Female's Health experienced difficulties in reaching of women invited for screening. In order to cope with this situation regional informational and educational campaign was developed. 50 volunteers distributed more than 20 000 leaflets with an appeal "Give love, not HPV" explaining basic things about HPV and its consequences as well as about how women might be protected against cervical cancer. It was also stated that each women in the age from 30-39 might undergo free of charge screening at her local Centre of Female's Health close to her home. Two regional TV channels and more than 50 bloggers have been involved into the campaign. Furthermore more than 120 regional gynaecologists were trained additionally by Federal Experts

#0427

9 - HPV screening

HUMAN PAPILLOMAVIRUS TESTING AS EXIT TEST FOR CERVICAL CANCER SCREENING AT AGE 60-64 YEARS: A DANISH REGISTER-BASED STUDY

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Background/Objectives: Until recently, all cervical screening in Denmark was undertaken with cytology at age 23-64 years. Several randomised controlled trials showed that HPV testing is substantially more sensitive for detection of high-grade intraepithelial cervical neoplasia (CIN2+) and more effective in preventing interval cancer.1 Encouraged by these findings, it was decided in 2012 to substitute cytology with HPV testing for women at their final screen at/or after age 60.2 Most randomised trials included women at age 60-64 years, but hardly any data were reported separately for this age group. We will describe the clinical outcomes for women aged 60-64 when HPV testing was rolled out within a routine screening program compared to women previously offered cytological screening.

Methods: The analysis was undertaken by using the national Danish pathology databank, Patobank including all pathology reports from 2006-2018 on women born between 1944-1956. This population-based study used routinely reported register data and we compared two cohorts of women at age 60-64 years, those who were screened with cytology and those who were screened with HPV testing. Our primary aim was to compare the detection of CIN2+, CIN3+ and cervical cancer in HPV+ women in up to two years after the baseline screen. The programming necessary to determine exposure and outcome was coded in R. Detailed criteria of exposure and outcome codes were prespecified in the protocol.

Results: In our sample there was 149.194 primary cytology screens and 120.651 primary HPV screens. The main analyses have been performed but are still lacking audit and quality check. It will be ready for presentation within a few weeks.

Conclusions: Conclusion is pending final quality check of data.

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#0312

9 - HPV screening

CLINICAL EVALUATION OF ALINITY M HR HPV ASSAY IN POPULATION-BASED CERVICAL CANCER SCREENING SETTING

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Background/Objectives: Alinity m HR HPV (Alinity; Abbott Molecular, Des Plaines, USA) is a novel assay that individually identifies genotypes HPV16, HPV18 and HPV45, while reporting 11 other high-risk HPV (hrHPV) genotypes in two distinct groups: HPV31/33/52/58 and HPV35/39/51/56/59/66/68. According to international guidelines, each HPV assay intended for clinical use should demonstrate predetermined thresholds of clinical accuracy in order to be eligible for use in HPV-based cervical cancer screening.

Methods: The clinical performance of Alinity was compared to Hybrid Capture 2 (hc2; Qiagen), RealTime High Risk HPV (RealTime; Abbott) and cobas 4800 HPV Test (cobas; Roche) in a representative set of samples obtained from Slovenian women 20-64 years old attending the routine organized national cervical cancer screening program, with over 70% national screening coverage. During the 2009/2010, 4,510 women were enrolled in the baseline screening round and after 36 months baseline screening participants were invited to the second round of screening between December 2012 and October 2014, using a similar approach.

Results: The clinical sensitivity and specificity for CIN2+ of Alinity in women aged ≥30 years were 100.0% (68/68; 95% CI, 92.2-100.0%) and 92.4% (2,844/3,077; 95% CI, 91.4-93.3%), respectively, and of hc2 95.6% (65/68; 95% CI, 87.6-99.1%) and 91.9% (2,829/3,077; 95% CI, 90.9-92.9%), respectively. At recommended thresholds of ≥98% and ≥90%, the clinical sensitivity and specificity ($p=0.0006$ and $p<0.0001$, respectively) of Alinity demonstrated noninferiority to hc2. In the ≥30 years age group, women who were baseline hrHPV-negative had lower risk for CIN2+ at 3 years using Alinity (0.04%) versus those with normal baseline cytology (0.65%) and comparable risk to that of RealTime (0.04%), hc2 (0.08%) and cobas 4800 HPV (0.04%). HPV16/18 infection was associated with a significantly higher baseline and 3-year CIN2+ and CIN3+ risk versus absence of HPV16/18 or presence of other hrHPVs at baseline (all p values <0.05). CIN2+ and CIN3+ risk at 3 years was significantly higher for the HPV31/33/52/58 channel of Alinity compared with the HPV35/39/51/56/59/66/68 channel (relative risk 3.5 [p=0.003] and 3.4 [p=0.03]), suggesting that extended genotyping of Alinity may be valuable in improving patient risk stratification. According to manufacturer's data Alinity's intra-laboratory and inter-laboratory reproducibility is 97.9% and 97.5%, respectively.

Conclusions: Alinity fulfils international consensus guideline criteria for primary cervical cancer screening and can be considered as clinically validated, demonstrating comparable safety to other clinically validated HPV tests.

#0045

9 - HPV screening

LIBUSE TRIAL - ALGORITHM FOR CERVICAL CANCER SCREENING IN THE CZECH REPUBLIC WITH USAGE OF HPV DNA TESTING WITH HPV 16/18 GENOTYPING AND P16/KI-67 DUAL-STAINED CYTOLOGY

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Background/Objectives: The incidence of cervical cancer in the Czech Republic remains stable over more than 30 years irrespective of existing national screening based on annual collecting of Pap smears. The aim of our prospective trial was to evaluate the role of HPV DNA testing with 16/18 genotyping and triage with p16/Ki-67 immunocytochemistry.

Methods: Women between 30 and 60 years who had in 12 collaborating centres regular annual Pap smear were co-tested for HPV DNA with selective 16/18 genotyping (Cobas 4800, Roche). All HPV 16/18 positive cases and/or those with severe abnormality in cytology were directly refered for colposcopy; HPV non-16/18 positive cases and LSILs were triaged using p16/Ki-67 dual-stained cytology (CINtec Plus, Roche) and positive cases were refered for colposcopy while negative cases were further followed.

Results: Altogether 2407 patiens were eligible for analysis after first round of screening. Mean age of subjects was 43 years. Pap smears showed 8 cases with severe and 105 cases with mild abnormalities. There were 7.4 % (180/2418) patients with HPV positivity, from which 50 had HPV 16 and/or 18. Biopsy confirmed 32 high-grade squamous and 2 glandular lesions, all of them were HPV positive. Triage using p16/Ki-67 was positive in 22.5 % cases (29/129).

Conclusions: Screening based on HPV testing with selective 16/18 genotyping and p16/Ki-67 triage found during the first round four times more high-grade lesions including glandular lesions than standard screening based on Pap smears.

#0323

9 - HPV screening

HPV 31 BASELINE PERFORMANCE AND RISK DETERMINATION FOR HIGH-GRADE CERVICAL DISEASE BY ONCLARITY DETECTION

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Background/Objectives: To determine performance results in women, ≥25 years, for human papillomavirus (HPV) primary screening (1° screening) with HPV 16/18/31-partial genotyping.

Methods: Of the 29,513women enrolled into the baseline phase of the Onclarity Trial, ≥age 25, those with atypical squamous cells-undetermined significance or worse cytology or a positive high-risk HPV result were referred to colposcopy/biopsy (5% normal cytology and HPV(-) also referred as controls). Performance values and odds ratios (OR) were calculated for cytology- and HPV-based screening using cervical intraepithelial neoplasia, grade 3 or worse (≥CIN3) adjudicated histology and standard statistical methods.

Results: Overall, 5,534 specimens had satisfactory histopathology. Individual HPV 16 (vs non-16), 18 (vs non-18), and 31 (vs non-31) carried OR of 11.8, 3.3, and 10.3, respectively, for ≥CIN3 histology. Positive likelihood ratios associated with ≥CIN3 for HPV 16, 18, and 31 were 5.9, 3.1, and 6.6, respectively. Inclusion of HPV 31 into an HPV16/18-1° screening algorithm improved sensitivity of detection for ≥CIN3 from 76.3 to 85.6; but required 212 more colposcopies (colpo/≥CIN3 ratio: 10.5 for 16/18-1°; 10.8 for 16/18/31-1°), the positive predictive value for 16/18-1° screening was 9.6% and for 16/18/31-1° screening was 9.3%.

Conclusions: Inclusion of HPV 31 in an HPV 16/18-1° screening algorithm is an effective approach to improve sensitivity for detection of ≥CIN3—but comes at a cost of increased colposcopies. Using the principles of equal management for equal risk, all parameters for HPV31 exceed the values for HPV18 and are similar to HPV16, suggesting that an optimal partial genotyping strategy should include HPV31.

#0368

9 - HPV screening

DNA vs RNA tests: update of the evidence

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Background/Objectives: Several countries are implementing primary HPV screening for prevention of cervical cancer. In 2015, in addition to the "golden standard" HPV DNA assays such as Hybrid Capture-II and GP5+/6+ PCR-EIA, the following five assays were classified as clinically validated for primary screening: Cobas 4800 HPV test, Abbott RealTime HPV test, PapilloCheck HPV-screening test, BD Onclarity HPV assay and the HPV-Risk assay [1]. Concerning HPV mRNA assays, only the Aptima HPV assay was classified as clinically validated but its performance among Aptima negative women over 5-year or longer screening intervals remained to be demonstrated [1]. The aim was to conduct an inventory of which HPV assays that were clinically validated for screening during the period between 2016 and 2019, according to the Meijer guidelines [2]. Another aim was to identify which HPV assays that are used in implemented HPV screening programs.

Methods: Literature search was conducted in PubMed to identify reports with "HPV validation primary screening 2016/2017/2018/2019" (up to 31 August 2019). A PubMed search for which HPV assays used in implemented primary HPV screening was performed by the use of the term "primary HPV screening population samples 2016/2017/2018/2019". Also other relevant studies of HPV screening assays were searched for in PubMed between 2016 and 2019.

Results: The following five HPV DNA assays, AnyplexTM II HPV HR, Xpert HPV assay, RealQuality RQ HPV screen, Cobas 6800 HPV test and HPVIR demonstrated clinical validity for primary HPV screening. The BD Onclarity HPV assay also showed clinical validity on SurePath screening samples. Concerning HPV mRNA assays, two studies reported similar high longitudinal negative predictive values (>99.7%) for absence of severe lesions during a 5-7 year follow-up period after negative Aptima results. Among implemented primary HPV screening programs, assays such as the Cobas 4800, the Hybrid Capture-II and the Aptima HPV mRNA assay were reported to be used.

Conclusions: Between year 2016 and 2019, five different HPV DNA assays were recognized as clinically validated for primary HPV screening. For the Aptima HPV mRNA assay, the demonstration of longitudinal protection over long periods implying that Aptima HPV mRNA testing can safely be used for cervical screening. Up to year 2019, in total 12 different HPV DNA assays and one HPV mRNA assay (Aptima) were clinically validated for primary HPV screening. Among implemented screening programs both HPV DNA and HPV mRNA (Aptima) assays are currently used.

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#0041

9 - HPV screening

Psychological effect of cervical cancer screening when changing primary screening method from cytology to high-risk human papilloma virus testing

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Background/Objectives: Between 2015 and 2018, Norway implemented high-risk human papilloma virus (hrHPV) testing in primary screening for cervical cancer, as a pilot project. In this project women aged 34-69 years and living in four Norwegian counties, have been pseudo-randomly assigned (1:1 randomization) to either hrHPV testing every 5 years (followed by cytology if hrHPV positive), or cytology testing every 3 years (followed by hrHPV testing if low-grade cytology). A concern with the introduction of the new screening method in Norway's national cervical cancer screening programme was whether the new screening method would lead to increased anxiety and depression among screening participants as compared to women screened with the conventional cell-sample. We therefore performed an ancillary study where we compared scores of anxiety and depression among screening participants by screening arm and screening results.

Methods: In total, 1,008 women answered a structured questionnaire that included the validated Patient Health Questionnaire-4 (PHQ-4), measuring anxiety and depression. The Relative Risk Ratio (RRR) of mild vs. normal anxiety and depression scores, and moderate/severe vs. normal anxiety and depression scores, were estimated by multinomial logistic regression with 95% confidence intervals (95% CIs).

Results: Compared to women who were screened with cytology, women randomized to hrHPV testing were not more likely to have mild anxiety and depression scores (RRR 0.96, CI 0.70-1.31) nor more likely to have moderate/severe anxiety and depression scores (RRR 1.14, CI 0.65-2.02). Women with five different combinations of abnormal screening test results were not more likely to have mild or moderate/severe vs. normal anxiety and depression scores than women receiving normal screening test results. The likelihood of having abnormal long-term (4-24 months after the screening) anxiety or depression scores among women 34 years and older was not affected by screening method or screening results.

Conclusions: The results of our study suggest that a change to hrHPV testing in primary screening for cervical cance will not increase psychological distress among participants and that screening participation is unlikly to decrase due to anxiety and depression.

#0348

34 - Economics and modelling

WHAT IS THE MOST COST-EFFECTIVE HPV-SCREENING METHOD IN EASTERN-EUROPE: THE EXAMPLE OF SLOVENIA

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Background/Objectives: As in most developed countries, Eastern European countries are contemplating to switch from cytology to the HPV-test as the primary screening test for their cervical cancer screening programme. However, it is unknown what the most cost-effective HPV-screening protocol is in that region. The aim of this study was to compare the costs, effects and cost-effectiveness of potential primary HPV screening protocols in Eastern Europe, using Slovenia as an example.

Methods: We calibrated the microsimulation model MISCAN to the Slovenian situation and simulated 896 HPV-screening protocols, which varied by starting, switching and end age, screening interval and the triage algorithm (i.e. cytology, HPV or genotyping). Main outcomes were quality adjusted lifeyears (QALYs) gained, total costs and incremental cost-effectiveness ratio (ICER). Costs and effects were discounted annually by 3% and the willingness-to-pay threshold (WTPT) was €50,000 per QALY gained. Univariate sensitivity analyses were performed on the costs of the HPV-test and on disutility weights.

Results: The optimal HPV screening protocol for Slovenia is 10-yearly screening from age 30 to 70 using genotyping and reflex cytology as a direct triage, referring all women with a high grade cytology result and women with HPV16/18 and a low grade cytology result to colposcopy. All other HPV-positive women are invited for a repeat HPV test after 12 months after which all HPV-positive women are referred to colposcopy (ICER = €48,390 per QALY gained). All efficient screening protocols contained genotyping and all screening protocols using screening intervals shorter than 7 years were dominated because the extra harms of screening would outweigh the benefits. Sensitivity analyses showed that increasing costs of the HPV-test decreased the optimal ending age to 60, while using different disutility weights decreased the optimal starting age to 27.

Conclusions: Both including genotyping in the triage algorithm and extending the screening interval to at least 7 years consistently resulted in a more favorable cost-effectiveness than strategies without genotyping and a shorter screening interval respectively. Applying the current 3-year screening interval will not gain more QALYs while this will incur more costs. Therefore, it is especially important to minimize opportunistic screening when implementing primary HPV screening, which might be more challenging if screening intervals are longer.

FC29 - Screening methods

#0080

9 - HPV screening

COMPARISON OF CO-TESTING AND PRIMARY HPV SCREENING STRATEGIES IN A POPULATION-BASED STUDY OF 2,627 WOMEN AGED 30 YEARS AND ABOVE

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Background/Objectives: Since regulatory approval of HPV detection methods in cervical cancer screening (CCS), there has been ongoing debate regarding the most optimal screening strategy. Some countries have implemented primary HPV screening, while others prefer co-testing until further evidence is available. We aim to compare cytology, HPV and co-testing strategies, and test performance using various HPV test cut-offs within a population-based study.

Methods: The MARZY cohort study was conducted between 2005 and 2012. Women aged ≥30 years (n=5,275) without hysterectomy or previous cervical cancer were invited to CCS with conventional Pap, liquid-based cytology (LBC, ThinPrep®) and HPV testing (Hybrid Capture®2, HC2). Participants positive for cytology with atypical squamous cells of undetermined significance or worse (ASC-US+) or high-risk HPV (hrHPV) positive with a viral load ≥1 RLU were referred to colposcopy. A random sample of test negatives (cytology normal & HPV negative) were also invited to colposcopy. For cross-sectional comparison, we calculated test performance (sensitivity, specificity), screening harms in excess colposcopies (number of women needed to undergo colposcopy (NNC) in order to detect 1 precancerous lesion or worse (CIN2+, CIN3+)) and rate ratios. Performance of HPV at higher cut-offs ≥3 and ≥10 RLU was assessed. Estimates were verification bias adjusted.

Results: We screened 2,627 women and prevalence of hrHPV was 6.3%. 620 women (222 positive: ASC-US+/hrHPV+; 398 negative: cytology & HPV) were referred, and 287 underwent colposcopy. Sensitivity of Pap and LBC for CIN2+ (47%) and CIN3+ (70%) was lower compared to HPV stand-alone (95% and 90% respectively). Co-testing of HPV and Pap or LBC showed highest sensitivity (CIN2+ 99%, CIN3+ 98%), but with loss of specificity (Pap co-testing: CIN2+ 93%, CIN3+ 92%; LBC co-testing: CIN2+ 95%, CIN3+ 94%). This was lower than stand-alone HPV testing at CIN2+ and CIN3+ (95% and 94% respectively), Pap (both endpoints: 97%) and LBC (99% and 98% respectively). The NNC required to detect 1 CIN2+ or CIN3+ was highest for Pap co-testing and similar for HPV stand-alone and LBC co-testing. When comparing rate ratios, co-testing was not superior to HPV stand-alone in sensitivity nor specificity. At higher HPV detection cut-offs, sensitivity at CIN3+ did not change at RLU≥3 but decreased at RLU≥10. Conversely, specificity increased to 96% and 97% for both RLU respectively.

Conclusions: Detection of CIN 2+ with cytology only is poor. When comparing HPV-based strategies, HPV stand-alone is equivalent to co-testing, but offers a better balance of benefits and harms. A higher HPV cut-off may be needed to minimise HPV-based harms in CCS.

#0349

14 - Screening methods

Preliminary data from a Swedish self- sampling study in postmenopausal women

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Background/Objectives: An updated screening algorithm was introduced in Sweden 2015. Primary HPV test for women >30 years old and a prolonged screening with the last test after 64 years of age were some of the changes. In the region of Örebro County, the previous cut-off age was 60 years and with a screening interval of 5 years, women left their last sample when they were 55-59 years old. In the shift between two screening programs, a group of women, 60-64 years old, that left the program 5-10 years ago were now included in the new screening. For re-inclusion, a two year long program was formed to catch-up this group of women and screen them according to the new screening algorithm. At the same time a research project investigating self-sampling was launched. At the same time as the women were invited for a last screening sample they were also asked to participate in a study where they should take a vaginal self-test up to one week after their ordinary screening sample was taken by a midwife.

Methods: Postmenopausal women between 64-70 years was included in the study. HPV status in samples from midwife sampling (MS) was compared to self-sampling (SS) samples. HPV was analyzed using HPV Aptima and all HPV positive samples, independent of sampling method, was triaged with cytology and followed-up according to national guidelines.

Results: So far, 585 women with paired samples have been included in the study. In the MS, 4% of the women are positive for hrHPV compared to 11% in the SS group. In 486/585 women, the results of the two samples are concordant. Among the non-concordant samples (13%), 62% were positive in SS and negative in MS. The opposite, negative in SS and positive in MS were seen in 4% of the samples. Among the MS negative samples, 32% were invalid in SS. Cytology was used as a triage test for HPV positive women, both for MS and SS. Of 23 hrHPV positive, 18 had normal cytology, 2 ASCUS, 1 LSIL and 1 HSIL. In the samples with abnormal cytology, 4/5 were hrHPV positive in both SS and MS. One sample was positive in SS but negative in MS.

Conclusions: In this age group, more women are hrHPV positive in SS compared to MS. This is in line with what other have seen. Among the very few hrHPV positive samples with abnormal cytology, the majority was hrHPV positive in both MS and SS. But since cytology is a poor triage marker in this age group clinical follow-up is needed before the effectiveness of the both sampling methods can be concluded.

#0382

14 - Screening methods

Primary HPV screening and cervical cytology in HIV-negative and HIV-positive South African women

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Background/Objectives: Cervical cancer causes the majority of cancer deaths in South African women, estimated at more than 4000 per year. The regional HIV epidemic has changed the epidemiology of HPV infections, cervical cancer precursors and cancer. Primary screening with HPV tests can reduce the cancer incidence but the strategy has mostly been evaluated in highly pre-screened populations with lower HPV and HIV prevalence. This study describes a cohort of 500 women, half of whom lives with HIV, who were tested by cervical cytology and a high-risk HPV test.

Methods: 500 women aged 25 to 64 with no screening in the preceding five years were included in this cohort, 250 from an HIV treatment clinic and 250 healthy women presenting for routine screening. Health care worker collected cervical samples were stored in liquid based cytology medium. A multichannel HPV DNA PCR test and cervical cytology were performed.

Results: 24 Participants were excluded from final analysis of which 22 (4.4% of total) was for no internal control on HPV test. HR HPV was detected more frequently in women living with HIV (39% vs 13%). Similarly, cytology was more frequently abnormal (ASCUS or above) in women living with HIV (33% vs 12%) as was the rate of high-grade and above cytology (17% vs 4%). 4 women with HIV (1.6%) had cytology suggestive of malignancy. 78% of women living with HIV had a negative HPV test. In those with normal cytology, HPV tested positive in 7.6% of HIV negative and 23.5% of HIV positive women.

Conclusions: Women living with HIV have high rates of HPV infection and cytological abnormalities. There is a high rate of HR HPV infection in women with normal cytology that indicate significant risk for the development of future pre-cancer or, alternatively, may indicate false negative cytology. This underestimation of risk by cytology may be far more serious in women living with HIV. Importantly, a significant proportion of women living with HIV were HR HPV negative and therefore qualify for less intense surveillance. The individual risk for underlying CIN2+ on histology associated with different HPV channels needs to be further explored.

#0630

14 - Screening methods

EXPANDING THE UPPER AGE LIMIT FOR CERVICAL CANCER SCREENING- A NATIONWIDE COHORT STUDY

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Background/Objectives: Cervical cancer screening programs in many countries including Denmark stop at the age of 64. However, an incidence peak of cervical cancer in women beyond the current screening age combined with the increasing female life expectancy has raised the question if the upper age limit should be changed to 69 years. This study, the first of its kind, evaluates the effect and feasibility of expanding the target population in the Danish cervical cancer screening program to include women aged 65 to 69 years. The study also evaluates if HPV self-sampling constitutes an appropriate supplementary screening method among older women.

Methods: The study is a nationwide population-based prospective cohort study. We consecutively include all 65 to 69 years old Danish women with no record of a cervical cytology sample or screening invitation within the last five years. Women unsubscribed from cervical cancer screening are excluded. Eligible women residing in the Central Denmark Region are allocated to the intervention group (n=20,000) and invited for HPV-based screening by having a liquid-based cervical cytology sample taken at the general practitioner (GP) or to request a self-sampling kit. Samples in the intervention group are analysed for HPV using the Cobas 4800 assay (Roche Diagnostics, Switzerland). Women residing in the other four Danish regions are allocated to the control group receiving standard care (n=71,500), which is no invitation for cervical cancer screening, but with the possibility to have an opportunistic sample taken at the GP in case of symptoms or other clinical indications. Outcomes in the intervention group are the proportion of targeted women participating by GP-based screening or self-sampling, HPV positivity rate, compliance to follow-up among HPV-positive self-samplers, proportion of abnormal cytological and histological findings, and the screening history of participants and non-participants. The following outcomes are compared between the intervention and control group: testing rate, proportion of abnormal cytological and histological findings, proportion of referrals for colposcopy/conization and the incidence and mortality of cervical cancer developed within 5 and 10 years.

Results: The study began in April 2019 and the study inclusion will be on-going in the next two years. For the intervention group preliminary results regarding the preferences of two screening methods will be presented.

Conclusions: This study provides new and important evidence allowing us to determine the effect including the pros and cons of expanding the upper age limit in an organized cervical cancer screening program.

#0653

20 - New technologies

Evaluation of Folate Receptor-mediated Tumor Detection as a Triage Tool for Cervical Cancer Screening

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Background/Objectives: To evaluate the triage performance of folate receptor-mediated tumor detection (FRD) for detection ofcervical high-grade lesions.

Methods:
A total of 1504 patients who had abnormal cytology results and/or positive human papillomavirus (HPV) testing during primary screenin FRD was applied before colposcopy to compare the detection rate, sensitivity, specificity, positive predictive value, negative predictive value, and coincidence rate according to the pathologic diagnosis in HPV positive and cytology of ASCUS population.

Results: To triage the HPVpositive population, the coincidence rate with pathology of FRD (66.67%) was higher than cytology ≥ASC-US (51.49%). The colposcopy referral rate of cytology and FRD as a triage tool was 969 (72.42%) and 736 (55.01%), respectively. Thus, the colposcopy referral rate decreased 233 (17.41%). To triage the ASC-US population, the coincidenc pathology higher than HPV (35.92%).

Conclusions: FRD could be used in the triage of the HPV-positive and ASC-US populations.

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#0435

14 - Screening methods

CLINICAL VALUE OF p16 IMMUNO-CYTOLOGY IN CERVICAL CANCER SCREENING: A POPULATION-BASED STUDY

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Background/Objectives: When used for cervical cancer primary screening, routine cytology has a high specificity but a lower sensitivity. For histological diagnosis of high-grade lesions, p16 immunostaining has proven to be useful. Therefore, our objective was to evaluate the use of PathCIN® p16INK4a immuno-cytology as a primary screen and as a secondary screen after primary screening with HPV testing.

Methods: A total of 5747 women were co-tested by liquid-based cytology and by HPV (Cobas4800) as part of a population based screening program. A total of 1097 cytology slides were examined by p16 immuno-cytology in two studies. In the primary screening study, 875 slides were randomly selected (without regard to HPV or cytology results) and analyzed for p16. In the triage study, 222 slides were chosen from the remainder according to HPV & cytology primary screening. All cytology slides were immuno-stained using PathCIN® p16INK4a antibody. The sensitivity and specificity for detection of CIN2+ were compared based on p16, cytology and HPV test results.

Results: For primary screening: p16 immuno-cytology is more specific than HPV testing and is similar in sensitivity. Also, p16 immuno-cytology compares favorably with routine cytology (≥ASCUS or ≥LSIL) in sensitivity and specificity. Combining routine cytology or HPV 16/18 testing with p16 immuno-cytology gave no increase in sensitivity and a decrease in specificity as compared to p16 alone. In screening for CIN2+, the values of Sensitivity, Specificity & Colposcopy Referral were: 95.4%, 82.5% & 73.4% for Primary HPV testing; 95.4%, 76.7% & 68.6% for Cytology ≥ASCUS; 76.9%, 89.7% & 47.1% for Cytology ≥LSIL; and 89.2%, 89.8% & 51.1% for p16 primary screen. In the triage study, the values of Sensitivity, Specificity & Colposcopy Referral were: 84.6%, 94.1% & 35.0% for p16 after HPV primary and 90.8%, 89.7% & 49.8% for ≥ASCUS after HPV primary. For secondary screening after primary HPV screening, p16 immuno-cytology is more specific than cytology. The calculated colposcopy referral rate is also decreased by using p16 immuno-cytology as triage after primary HPV screening. In combining the primary screening study and the triage study, there were 331 cases with histopathology including 65 cases with CIN2+ and 266 <CIN2 (1 CA, 33 CIN3, 31 CIN2, 37 CIN1, & 229 NILM). Among the 243 cases positive for HPV, 62 were CIN2+ and 181 were <CIN2. Of the 85 HPV 16/18+ cases, 24 were CIN2+ and 61 were <CIN2. There were 156 cases ≥LSIL/AGC, of which 50 were CIN2+ and 106 were <CIN2. There were 71 ASCUS cases of which 12 were CIN2+ and 59 were <CIN2. There were 163 cases positive by p16 immuno-cytology, including 58 CIN2+ (1/1 CA, 31/33 CIN3, 26/31 CIN2) and 105 <CIN2 (18/37 CIN1 & 87/229 NILM). The p16 positivity rate increased with histologic severity ($P<0.001$).

Conclusions: For primary screening, p16 immuno-cytology compares favorably to routine liquid-based cytology and HPV testing. Immunostaining of cytology slides with p16INK4a antibody could be an effective primary screening method and could also be an efficient triage to reduce the colposcopy referral rate after primary HR-HPV screening. Therefore, PathCIN® p16INK4a may be applicable as a favorable technology for large-size population-based screening.

#1062

14 - Screening methods

IMPACT OF HPV STATUS KNOWLEDGE ON CYTOLOGY REVISION (CO-TEST COHORT)

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Background/Objectives: Co-testing for cervical cancer screening is widely used in opportunistic screening and is still recommended by the ASCCP as the preferable approach (Saslow et al., 2012). Nevertheless some authors state that the added value of cytology plus the hr-HPV testing benefits fewer women (Schiffman et al., 2018) and therefore compromises the cost-effectiveness of the screening methodology. This is the main reason why hr-HPV test alone is the preferred approach in organized screening programs, especially in Europe. The laboratory receives liquid cytology samples for opportunistic screening, some clinicians use co-testing to screen their patients. In this cohort, it is a laboratory quality control practice in LAP to review the cytology if negative (<ASCUS) and hr-HPV positive or vice versa. The purpose of this work is to evaluate whether the cytotechnicians and cytopathologists are influenced reviewing cases knowing already the HPV status.

Methods: Data from January 2017 to August 2019 was collected from the laboratory data base, a total of 1595 cases. The laboratory uses the Bethesda System Classification, has a sensitivity of 91,7% in monolayer cytology and an ASCUS percentage of 4,7%.

Results: Resumed data analysis shows 18,45% upgraded cytology results and only 5,07% downgraded. When HPV 16 is positive, this number increases and 26,13% were upgraded. The number of cases classified as NILM were reduced from 1301 to 1100 (15,4%), as 21,8% were upgraded to ASC-US or higher. Furthermore, 57,7% of the cases classified as ASC-US remained ASC-US and 38,1% were downgraded to NILM. Of the 4,2% ASCUS cases upgraded, 1,1% were reclassified as ASC-H or HSIL and HPV 16 was involved. Additionally, there were identified 22 cases of LSIL with HPV negative (5 above 50 years old).

Conclusions: Preliminary data analysis clearly shows that some substantial impact exists on the slide revision with hr-HPV status consciousness, and it is a "real life" example of what some authors already predicted (Richardson et al., 2015)(Jr, Stoler, Aslam, & Behrens, 2016). Another consideration is that in this cohort the co-testing allowed the redefinition of the risk assessment of 5 HPV negative cases, due to the cytology result.

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