CRN - case number 2

Institution: The Cancer Registry of Norway (CRN)
Administrative unit: The Cancer Registry of Norway (CRN)
Title of case study: Accelerating cervical cancer elimination: Research-driven innovations in Prevention
Period when the underpinning research was undertaken: 2012 and onwards
Period when staff involved in the underpinning research were employed by the submitting institution: Post-docs were employed during 2015-2022. Several permanent employees have also been involved
Period when the impact occurred: 2017 and onwards

1. Summary of the impact (indicative maximum 100 words)

The establishment of a causal link between human papillomavirus (HPV) infection and cervical cancer has driven the development of new technologies for integration into existing cervical cancer prevention policies. Based on our research, the following changes have been implemented in the Norwegian screening programme, CervicalScreen Norway:

A) HPV-based screening was implemented for women over 34 years in 2017
B) screening algorithms for HPV-positives were improved using partial HPV genotyping in 2018
C) self-sampling is currently under implementation

D) Furthermore, our public-private research collaboration on long-term effectiveness and safety of HPV vaccines has had wide reaching implications, influencing decisions regarding the need of booster doses years after HPV vaccination.

2. Underpinning research (indicative maximum 500 words) **Key research and aims:**

Below we focus on studies that have had a direct impact on decisions/policies made for the CervicalScreen Norway and for HPV vaccination programmes beyond Norway.

A) **Navigating change: Gradual and controlled replacement of cytology with HPV-testing in screening for women older than 34 years of age in Norway.**
Cytology-based cervical cancer screening was pivotal in reducing cervical cancer incidence in Norway from the 1970s. From 2006 and onwards, several randomized controlled trials have demonstrated that HPV based screening is more sensitive than conventional cytology-based screening. However, the replacement of screening technology on a large scale requires significant modifications to existing infrastructure and protocols in the screening programme (including staff training, follow-up algorithms, communication). To minimize adverse effects, we performed a gradual and randomized implementation of HPV testing in CervicalScreen Norway.(1).

B) **Balancing act: How to ensure equal management for women with equal risk for cervical cancer?** Commercially available HPV assays used in screening detect 14 high-risk (hr) HPV genotypes. While these HPV-assays are more sensitive than cytology exams in screening, they cannot differentiate between clinically irrelevant transient HPV infections and persistent HPV infections that can lead to cancer. Until recently, all HPV-positive samples have been additionally tested for cellular changes to identify individuals with underlying precancers or cancers. However, referring all women with abnormal results to colposcopy and biopsy, resulted in suboptimal clinical management algorithm with low positive

predictive value (1), leading to excessive use of health care services as well as distress among women. In our effort to calibrate the follow-up algorithm, we relied on the premise that each of the 14 distinct hr HPV genotypes possesses its own unique carcinogenic potential and cervical cancer risk profile. Our study assessed the harms and benefits associated with HPV genotype specific algorithms by following up more than 3000 hrHPV positive women (2).

C) **Breaking barriers: HPV self-sampling as an alternative to physician-performed sampling.** Among the various reasons why a significant number of women do not attend cervical screening at recommended intervals, are negative past experiences related to pelvic exams, practical barriers, and, at times, a painful history of sexual abuse**.** Collecting the screening samples at home by the women themselves for HPV testing, can mitigate some of these barriers. The usefulness of HPV testing on self-collected samples for screening programmes rests on at least two assumptions: i) comparable sensitivity in detecting cervical cancer and precancers between self-sampling and physician-based sampling, and ii) increased participation in screening with self-sampling compared to physician sampling. The CRN has performed several studies to evaluate i) and ii) (3,4,)

D) **Beyond the clinical trial: HPV vaccines' prolonged impact.** in a long-term follow-up of the HPV vaccine targeting four HPV genotypes (HPV6, HPV11, HPV16, HPV18), this vaccine was found to be highly effective in preventing cervical precancers caused by these four targeted HPV types in a pivotal phase 3 study. This vaccine is used in national HPV vaccination programmes across the globe. However, the original phase 3 study, with a four-year follow-up, was insufficient to determine whether vaccination at age of 12 years provides life-long protection against HPV. In our later study the phase 3 trial was extended over 14 years, involving continued follow-up of 5493 women from Denmark, Iceland, Norway and Sweden. The aim was to evaluate the long-term effectiveness and safety through national registries, cancer screening programmes, and biobanks (5).

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these times are stated).

Mari Nygård, Senior researcher at the Department of Research, and Head of Department since 2020, led the evaluation of the implementation of primary HPV-based screening (1), was the senior researcher in the study on improving the screening algorithm based on partial genotyping (2), PI of the self-sampling study described in (3), was heavily involved in the randomized controlled trial on self-sampling (4), and was the Norwegian PI in the long-term follow-up study of HPV vaccine (5).

Ameli Tropé, Head of Section of cervical cancer screening (2015–) led the implementation of primary HPV-based screening (1), was involved in the study on improving the screening algorithm based on partial genotyping (2), and in randomized controlled trial on self-sampling (4).

Birgit Engesæter, Senior Advisor, Section of cervical cancer screening (2015-) co-led the implementation of primary HPV-based screening(1), and improving the screening algorithm based on partial genotyping (2).
Bo Terning Hansen, Researcher, Department of Research was PI of the randomized controlled trial on self-sampling (4).
Dana Hashim, Section for cervical cancer screening (2017-2018) was the first author of (2).
Maarit Leinonen, Postdoc, Department of Research (2015-2019) was the first author of (3).
Gunvor Aasbøe, Postdoc, Department of Research (2017-2023), was the first author of (4).

Other employees from the CRN were also involved. They have been employed throughout the period 2012–2022, unless otherwise stated:
Philip E Castle, Senior Advisor (part-temporary, 2014)
Sophie Berger, Senior advisor, from 2022: Head of Section of Administration and Research Support, Department of Research
Espen Enerly, Researcher, Department of Research
Suzanne Campell, Advisor, Department of Research
Kristina Schee, Advisor, Department of Research (2013-2016)

Since 2009, research on HPV-related cancers and prevention opportunities at CRN has been conducted through the HPV Research Group, as well as by the Section of Cervical Cancer Screening.

3. References to the research (indicative maximum of six references)

1. Nygard, M, Engesaeter B, Castle PE, Berland JM, Eide ML, Iversen OE, Jonassen MC, Christiansen IK, Vintermyr OK, Tropé A. Randomized Implementation of a Primary Human Papillomavirus Testing-based Cervical Cancer Screening Protocol for Women 34 to 69 Years in Norway. Cancer Epidemiol Biomarkers Prev, 2022. 31(9): p. 1812-1822. OA https://doi.org/10.1158/1055-9965.epi-22-0340

2.Hashim, Engesæter B, Skare G, Castle P, Bjørge T, Tropé T, Nygård M. Real-world data on cervical cancer risk stratification by cytology and HPV genotype to inform the management of HPV-positive women in routine cervical screening. Br J Cancer, 2020. 122(11): p. 1715-1723. OA: https://www.nature.com/articles/s41416-020-0790-1

3. Leinonen M, Schee K, Jonassen C, Lie A, Nystrand C, Rangberg A, Furre I, Johansson M, Tropé A, Sjøborg K, Castle P, Nygård M. Safety and acceptability of human papillomavirus testing of self-collected specimens: A methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. J Clin Virol, 2018. 99-100: p. 22-30. Free article: https://www.sciencedirect.com/science/article/pii/S1386653217303475?via=ihub

4. Aasbo G, Trope A, Nygard M, Christiansen IK, Baasland I, Iversen GA, Munk AC, Chriastiansen MH, Undem K, Bjørge T, Castle P, Hansen BT. HPV self-sampling among long-term non-attenders to cervical cancer screening in Norway: a pragmatic randomised controlled trial. BrJCancer,2022.**127** (10):p.1816-1826.OA: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9643532/pdf/41416_2022_Article_1954.pdf

5. Kjaer SK, Nygård M, Sundström K, Dillner J, Tryggvadottir L, Munk C, Berger S, Enerly E, Hortlund M, Ágústsson AI, Bjelkenkrantz K, Fridrich K, Guðmundsdóttir I, Sørbye SW, Bautista O, Group T, Luxenbourg A, Mershall JB, Radley D, Yang YS, Badshah C, Saah A. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. EClinicalMedicine, 2020. **23**: p. 100401. OA: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30145-0/fulltext -

4. Details of the impact (indicative maximum 750 words)

The ultimate goal of our research is to provide the best possible cervical cancer prevention options for Norwegian women, and to contribute knowledge that advances cervical cancer prevention globally. Our group is well-positioned for these tasks thanks to our existing comprehensive registry data on the cervical cancer screening programme dating back to 1991, which includes detailed information on over 14 million screening exams by more than 1.8 million women. Our flexible registry solutions enable us to assess the real-life impact of rapidly expanding pool of technologies available to enhance cervical cancer screening.

The underpinning research described in section 2 has given support for policy decisions for the cervical cancer screening programme, as well as for HPV vaccination strategies, in Norway and globally.

A) Gradual implementation of HPV-based screening in Norway for women older than 34 years of age in 2017. The 77,207 women randomized to HPV screening and 80,240 to cytology screening were followed up from 2015 to 2017, demonstrating that HPV screening was well accepted and that HPV -based screening detected 40% more cancers and 60% more pre-cancer than cytology (1). Similarly, a large study in the UK detected 50% more precancers and 30% more cancers in HPV-screening as compared to cytology (6). The UK study, along with the meta-analysis of randomised controlled studies (7) document a very low incidence of cervical precancers and cancers among HPV-negative individuals, supporting an extension of the 3-years screening interval. In summary, supported by international research, our study results provided the main scientific evidence underpinning the decision taken in 2017 to implement primary HPV-based screening to all women 34-69 years of age in Norway.

B) Partial HPV genotyping was implemented for HPV-positives in 2018. In the HPV-based screening that was implemented in 2017, all hrHPV-positive women with abnormal cytology were referred to colposcopy and biopsy which resulted in 60% higher rates for colposcopy referrals. A similar concern has been raised by cervical cancer screening programme coordinators from other countries. Our study demonstrated that separating the most carcinogenic genotypes, HPV16 and 18, from the pool of the remaining hrHPV types by partial genotyping, will stratify women according to risk for cervical cancer (in combination with cytology). This calibration of screening algorithm reduces unnecessary colposcopy referrals with biopsy for women with lower precancer or cancer risk. Our article was thoroughly discussed in an editorial by Arbyn et al., who emphasized both the importance of, and lack, of real-world studies assessing the colposcopy referral algorithms (8). This is much needed information, as the HPV-based primary screening programmes continue to evolve. Based on our research, the follow-up algorithm for HPV-positives was changed in July 2018 (2). In the historical overview of CervicalScreen Norway given in Bjørge et al, this and other changes in the screening programme is described (9).

C) Implementing self-sampling in the cervical screening programme from 2021. The CRN studies showed that (i) compared with physician-taken samples for detecting the presence of HPV DNA among women with cervical cancer and precancers, the self-sampling performed equally well. Our randomized controlled trial performed in the CervicalScreen Norway demonstrated 23% higher participation rate among long-term non-attending women who got a self-sampling kit by mail as compared to those who received a regular invitation, (ii) suggesting that self-sampling increases screening participation among those who do not attend regularly. Similar results from Sweden and Denmark were reported (10,11). Furthermore, in collaboration with a group of modelling experts at the University of Oslo and Harvard University, we assessed the cost-effectiveness and consequences of implementing self-sampling in CervicalScreen Norway. Those findings suggest that targeted self-sampling for those not attending screening likely provides a cost-effective solution (12). Supported by these studies, the CervicalScreen Norway decided in 2021 to implement self-sampling into the programme to boost participation among long-time non-attenders. In 2022, 20.5 million Norwegian kroner (NOK) were allocated over the National budget, and an additional 19.2 million NOK were allocated in 2023, for further implementation of self-sampling in the screening programme.

D) No need for a booster dose for those vaccinated with a three-dose regimen The long-term follow-up of Nordic women demonstrated 100% effectiveness during the follow-up of 14 years, with no high-grade cervical dysplasia caused by the HPV types targeted by the vaccine. The study found no evidence of waning immunity over this time period. The effectiveness results were consistent with prolonged and sustained immunity against the vaccine-related HPV types. The study has thus demonstrated that within 14 years there should be no need for a booster dose. Similar results are also available for the other HPV vaccine (13). Supported by these data, no countries have yet implemented any programme for revaccination of fully HPV-vaccinated individuals (14).

5. Sources to corroborate the impact (indicative maximum of ten references)

Navigating change: gradual and controlled replacement of cytology with HPV-testing in screening for women older than 34 years of age in Norway.

6. Rebolj M, Rimmer J, Denton K, Tidy J, Mathews C, Ellis K, Smith J, Evans C, Giles T, Frew V, Tyler X, Sargent A, Parker J, Holbrook M, Hunt K, Tidbury P, Levine T, Smith D, Patnick J, Stubbs R, Moss S, Kitchener H. Primary cervical screening with high risk human papillomavirus testing: observational study. BMJ 2019;364:l240. OA: https://www.bmj.com/content/364/bmj.l240

7. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet, 2014. **383**(9916): p. 524-32 Link web: https://www.sciencedirect.com/science/article/pii/S0140673613622187?via=ihub

B) Balancing Act: how to ensure equal management for women with equal risk for cervical cancer?

8. Arbyn M, Yuill RS, Canfell K. Triage of HPV-positive women in Norway using cytology, HPV16/18 genotyping and HPV persistence. Br J Cancer, 2020. 122(11): p. 1577-1579. OA: https://www.nature.com/articles/s41416-020-0787-9

9. Bjørge T, Engesæter B, Skare GB, Tropé A. *CervicalScreen Norway – A screening programme in transition*. Norsk Epidemiologi, 2022. 30(1-2) DOI: https://doi.org/10.5324/nje.v30i1-2.4978

C) Implementing self-sampling in the cervical screening programme.

10. Elfström KM, Sundström K, Andersson S, Bzhalava Z, Carlsten Thor A, Gzoul Z, Öhman D, Lamin H, Eklund C, Dillner J, Törnberg S. Increasing participation in cervical screening by targeting long-term nonattenders: Randomized health services study. Int J Cancer. 2019 Dec 1;145(11):3033-3039. Fee access: https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.32374

11. Lam JU, Rebolj M, Møller Ejegod D, Pedersen H, Rygaard C, Lynge E, Thirstrup Thomsen L, Krüger Kjaer S, Bonde J. Human papillomavirus self-sampling for screening nonattenders: Opt-in pilot implementation with electronic communication platforms. Int J Cancer. 2017 May 15;140(10):2212-2219. OA: https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.30647

12. Burger EA, Sy S, Nygård M, Kim JJ. The Cost-Effectiveness of Cervical Self-Sampling to Improve Routine Cervical Cancer Screening: The Importance of Respondent Screening History and Compliance. Cancer Epidemiol Biomarkers Prev. 2017 Jan;26(1):95-103. Link to website: https://aacrjournals.org/cebp/article/26/1/95/71127/The-Cost-Effectiveness-of-Cervical-Self-Sampling

D) No administration of a booster dose for those vaccinated with a three-dose regimen at the age of 12

13. World Health Organization, *Human papillomavirus vaccines: WHO position paper (2022 update).* Weekly epidemiological record, 2022. **50**(97): p. 645-672. Link to website: https://www.who.int/publications/i/item/who-wer9750-645-672

14. Mariz FC, Gray P, Bender N, Eriksson T, Kann H, Apter D, Paavonen J, Pajunen E, Prager KM, Sehr P, Surcel HM, Waterboer T, Müller M, Pawlita M, Lehtinen M. Sustainability of neutralising antibodies induced by bivalent or quadrivalent HPV vaccines and correlation with efficacy: a combined follow-up analysis of data from two randomised, double-blind, multicentre, phase 3 trials. Lancet Infect Dis. 2021 Oct;21(10):1458-1468. Link: https://www.sciencedirect.com/science/article/pii/S1473309920308732?via=ihub